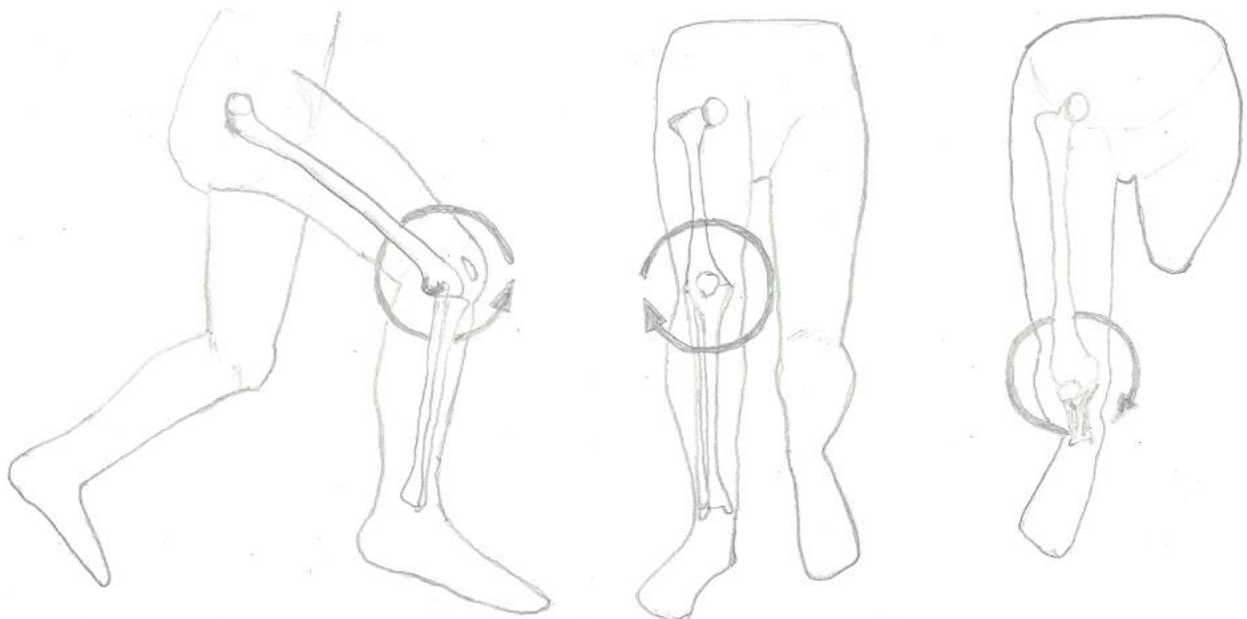


Neuromuscular exercise as treatment for knee osteoarthritis in middle aged patients

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PhD Thesis 2016



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Fejl! Bogmærke er ikke defineret.

Preface

This PhD thesis was accomplished at the Department of Sports Science and Clinical Biomechanics, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark. The main supervisor was Professor Ewa M. Roos from the Research Unit for Musculoskeletal Function and Physiotherapy and co-supervision was provided by Associate Professor Anders Holsgaard-Larsen, the Orthopaedic Research Unit, Department of Orthopaedics and Traumatology, Odense University Hospital (OUH), Odense, Denmark.

The study subjects were recruited via primary care general practitioners (GPs) in the communities of Odense and Middelfart, Denmark, and from advertisements in local clubs, libraries, print media, and Facebook. Outcome assessments at baseline and after treatment were carried out at the motion analysis laboratory at OUH, Odense, Denmark.

The studies contained in this thesis were funded by the Region of Southern Denmark PhD fund, €67,000; the Region of Southern Denmark research fund, €67,000; a University of Southern Denmark scholarship, €55,000; Odense University Hospital free research funds, €44,000; The Danish Rheumatism Association, €42,000; The Association of Danish Physiotherapists, €5,000; Family Hede Nielsens fund, €2,600; and a Danish Rheumatism Association Ryholts grant, €2,000. None of the funders have any role in the study other than to provide funding.

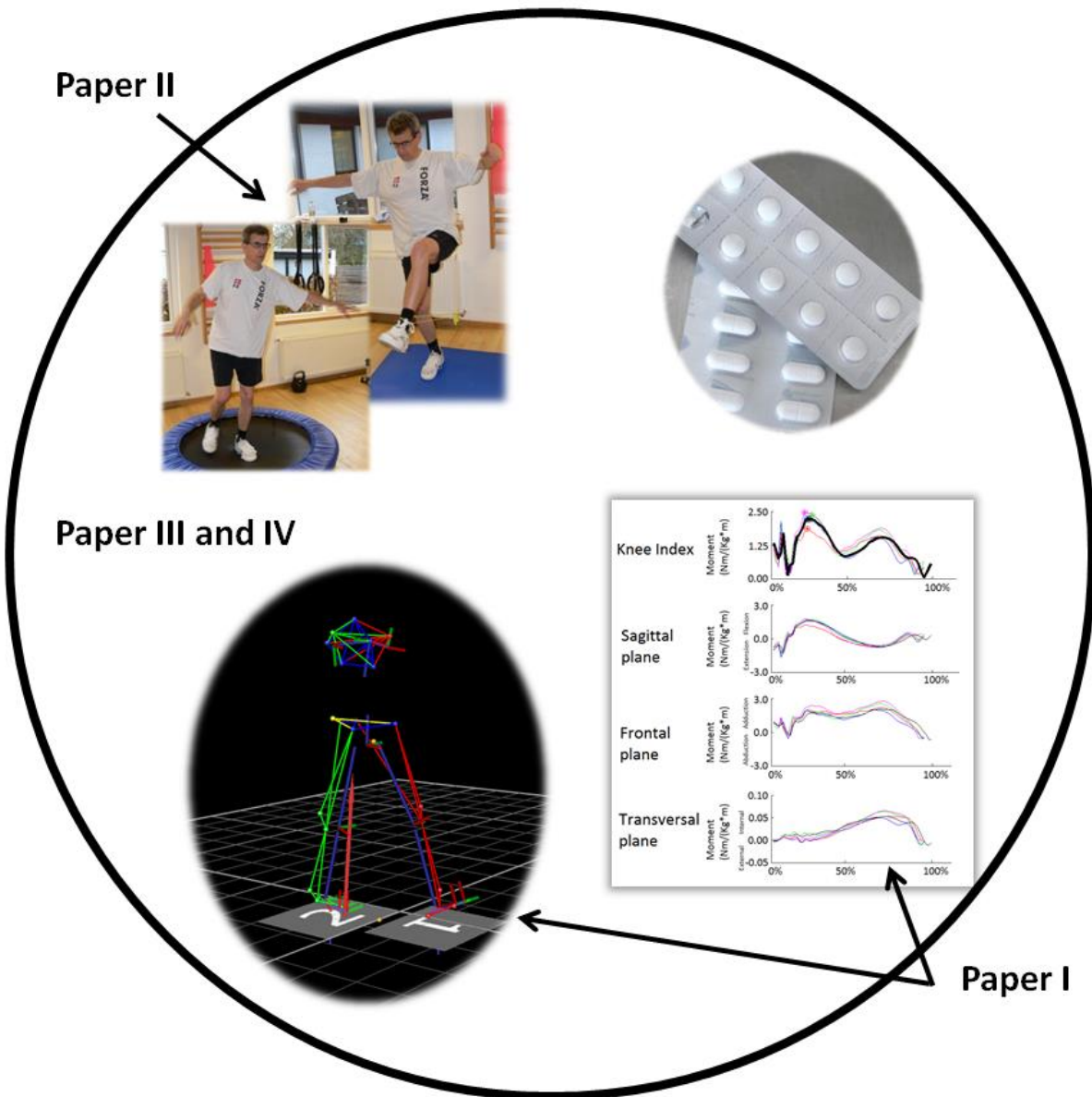
List of papers

This thesis is based on the following four papers, which will be referred to by their Roman numerals in the text:

- I. Clausen B, Andriacchi T P, Nielsen D B, Roos E M, Holsgaard-Larsen A. The Knee Index and its composition – a novel measure of knee joint load in subjects with mild to moderate knee osteoarthritis. In manuscript
- II. Clausen B, Holsgaard-Larsen A, Roos E M. An 8-week Neuromuscular Exercise Program in Middle-aged Subjects with Mild to Moderate Knee Osteoarthritis – a Case-series. Submitted
- III. Clausen B, Holsgaard-Larsen A, Søndergaard J, Christensen R, Andriacchi T P, Roos E M. The effect on knee-joint load of instruction in analgesic use compared with neuromuscular exercise in patients with knee osteoarthritis: study protocol for a randomized, single-blind, controlled trial (the EXERPHARMA trial). *Trials* 2014; 15:444
- IV. Holsgaard-Larsen A, Clausen B, Søndergaard J, Christensen R, Andriacchi T P, Roos E M. The effect on knee-joint load of instruction in analgesic use compared with neuromuscular exercise in patients with knee osteoarthritis: a randomized, single-blind, controlled trial (the EXERPHARMA trial). In manuscript

Thesis at a glance

This thesis comprises four studies describing the design and quality assurance of a randomized controlled trial evaluating two different pain relief interventions for subjects with mild to moderate knee osteoarthritis (OA). Paper I reported the properties of a novel biomechanical variable, the Knee Index, for evaluating total knee joint load. Paper II reported the feasibility of the neuromuscular exercise intervention for subjects with mild to moderate knee OA. Paper III described the protocol for the randomized controlled trial evaluating the effect on knee joint load of two pain relief interventions: neuromuscular exercise or drug use. Paper IV reported the effectiveness of the two pain relief interventions: neuromuscular exercise or drug use.

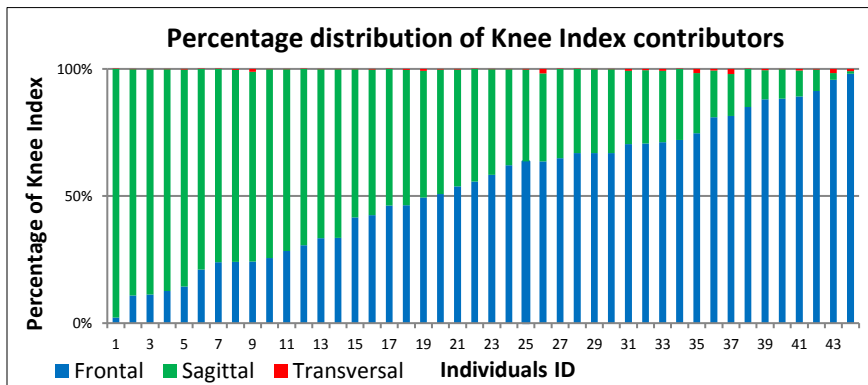


Paper I – Is a novel measure of knee joint load, the Knee Index, suitable for use as a primary outcome in a randomized controlled trial?

Subjects: The first 44 subjects (23 females) with a mean age 57.5 years, included in the EXERPHARMA trial.

Method: A cross-sectional study. Using three dimensional gait analysis, we describe a novel biomechanical index of knee joint loading in patients with mild to moderate knee OA by reporting: i) the relative contribution and inter-subject variation of each plane to the Knee Index, and ii) how other biomechanical variables may be associated with the Knee Index.

Conclusion: Despite large variation in the composition of the Knee Index, it was primarily composed of the frontal and sagittal planes, indicating that some subjects with mild to moderate knee OA have a movement strategy dominated by frontal or sagittal moment. Depending on the knee-loading strategy, the Knee Index was associated with both the frontal and sagittal planes. The current results hold promise for the Knee Index as both a sensitive and responsive biomechanical outcome.



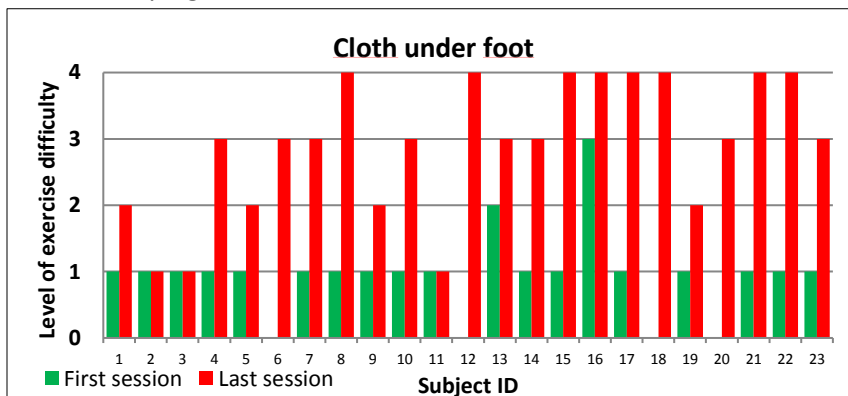
Between-subject variation: percentage distribution of the contributors to the Knee Index (study knee) in the 44 individuals. Individuals are ordered from lowest to highest for frontal plane contribution – Mean of 5 trials.

Paper II – Is a neuromuscular exercise program (NEMEX-KOA) a feasible intervention for subjects with mild to moderate knee OA?

Subjects: The first 23 (12 females) subjects undergoing an 8-week neuromuscular exercise program.

Method: A case-series study describing the feasibility of a NEMEX program (NEMEX-KOA) in terms of progression in exercise, exertion, pain, adverse events, and adherence to exercise for subjects with mild to moderate KOA.

Conclusion: In subjects with mild to severe pain in activity at baseline, NEMEX-KOA was found feasible. Progression was achieved with few incidents of clinically relevant increase in pain and no adverse events. Jumping activities were, however, not feasible.



Paper III – A protocol for a randomized controlled trial on two pain-relieving treatments for mild to moderate knee OA. The EXERPHARMA trial.

Subjects: 100 subjects, aged 40-70 years with mild to moderate knee OA, Kellgren and Lawrence grade 0-3, were to be recruited.

Method: A protocol describing a randomized controlled trial, evaluating the effectiveness of neuromuscular exercise and optimized use of analgesics and anti-inflammatory drugs, on measures of knee joint load during gait, patient-reported outcomes and functional performance in subjects with mild to moderate knee OA.

Conclusion: The results of the EXERPHARMA trial will help to determine whether 8 weeks of neuromuscular exercise is superior to optimized use of analgesics and anti-inflammatory drugs regarding knee joint load, pain and functional performance in individuals with mild to moderate knee OA.



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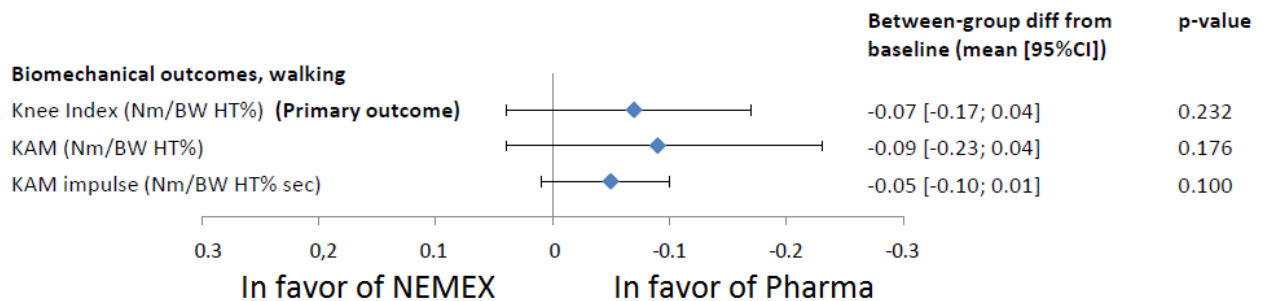


Paper IV – The effect on knee joint load of instruction in analgesic use compared with neuromuscular exercise in patients with knee osteoarthritis: a randomized, single-blind, controlled trial (the EXERPHARMA trial).

Subjects: 93 subjects (85% women, 58 ± 8 years with a BMI of 26.9 ± 3), were randomized to either the NEMEX-group (n = 47) or the Pharma-group (n = 46). Data from 44 and 41 patients, respectively, were available at follow-up. Subjects were recruited from July 2012 to May 2015.

Method: In a randomized, single-blind, controlled trial, we compared the effectiveness of neuromuscular exercise (NEMEX-group) to optimized analgesics and anti-inflammatory drugs (Pharma-group), on measures of knee joint load during gait, patient-reported outcomes and functional performance in individuals with mild to moderate knee OA.

Conclusion: The EXERPHARMA trial evaluated the possible joint load modifying effects of a neuromuscular exercise program compared with information on the recommended use of analgesics and anti-inflammatory drugs. Due to poor adherence, especially in the Pharma-group, and a similar intake of pain relief medication in both groups, we essentially compared the addition of 8 weeks of neuromuscular exercise to ‘care as usual’, which did not result in reduced knee joint load during walking.



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Abbreviations and definitions

ACR: American College of Rheumatism

ADL: Activities of Daily Living

BW: body weight

CR-10: Borg's category ratio scale

GP: general practitioner

HT: height

KAM: knee adduction moment

KFM: knee flexion moment

KL: Kellgren and Lawrence

KOOS: Knee injury and Osteoarthritis Outcome Score

Knee Index: corresponds to 1st peak Knee Index

MDC: minimal detectable change

NEMEX: NEuroMuscular EXercise

NSAID: nonsteroidal anti-inflammatory drug

OA: osteoarthritis

OUH: Odense University Hospital

Pharma: pharmacologic treatment

QOL: quality of life

SD: standard deviation

Study knee: Most affected knee, or dominant if equally affected

VAS: Visual Analog Scale

Introduction

Knee osteoarthritis (OA) is a degenerative joint disease, which alters the structure of the cartilage [4, 5]. The cartilage degenerates along with the surrounding tissue, that is, the synovial membrane, menisci and underlying bone. Over time, knee OA will cause both pain and loss of physical function, resulting in reduced quality of life [6].

Prevalence

On a global level, it was estimated that there were 241 million cases of OA in 2013, which was a 71.9% increase from 1990 [7]. The global age-standardised prevalence of knee OA was 3.8% in 2010 and was a little higher in women than men. Hip and knee OA was ranked as the 11th highest contributor to global disability out of 291 conditions [8]. With increasing age and more people being overweight in the population, the prevalence of OA is likely to rise in the future [8]. About one third of individuals with knee OA will experience progression to more advanced disease [9, 10], which is the leading indication for knee replacement surgery.

Diagnosing knee OA

Historically, diagnosis and severity of knee OA have been based on structural changes as seen on plain radiographs of the tibiofemoral joint. Knee radiographs are commonly graded by the Kellgren and Lawrence (KL) grading system [13, 14]. However, radiographs have been found to be an imprecise guide for diagnosing knee OA, in that there is poor correlation between pain and structural changes [15,

Table 1: Criteria for diagnosing Knee OA developed by ACR and EULAR [11, 12].

Risk factors:	Symptoms:	Objective examination:
Age >40 years	Persistent knee pain	Crepitus during active movement
Female	Brief morning stiffness	Bony tenderness
Overweight	Functional limitations	Bony enlargement
Occupation	Acute knee pain	Palpable effusion
Family history of OA		No palpable warmth
		Restricted movement
		Joint instability

16]. This thesis defines knee OA based on the clinical picture and examination, using the two sets of criteria developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatism (ACR) (Table 1) for the diagnosis of knee OA consisting of risk factors, symptoms and objective examination [11, 12].

A clinical examination including symptoms, functional performance and patient willingness, together with a plain radiograph of the tibiofemoral joint is the typical tool used for assessing possible need for end-stage treatment of knee OA, for example, tibial osteotomy or total knee joint replacement [17]. However, from a patient perspective, pain is the single most important factor in the decision to undergo knee joint replacement surgery [17].

Treatment of knee OA

Clinical guidelines advocate non-drug treatments as first line treatment for knee OA and as such, they should be offered to all patients with knee OA [18-20]. These include education, exercise and weight loss, and are preferred for their anticipated negligible adverse effects while still having relevant clinical efficacy (Figure 1). Second line treatments are needed by some and include treatments such as pharmacological pain relief, walking aids and passive treatments (e.g. manual therapy, acupuncture and other treatments given by a therapist and not requiring an active lifestyle change). Finally, third line treatments are only relevant for a few and include surgery, such as knee joint replacement surgery [3].

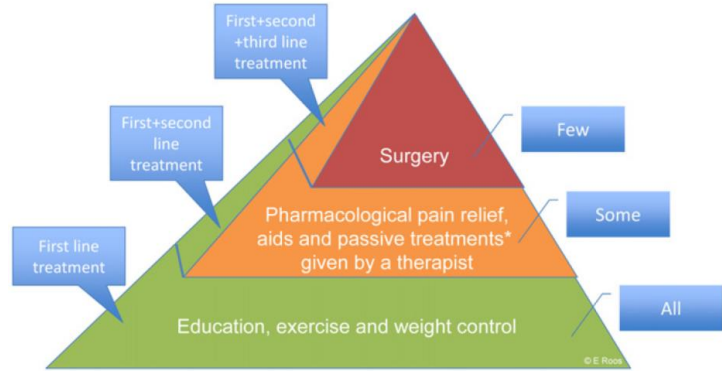


Figure 1: The OA treatment pyramid [3].

Second line treatments are needed by some and include treatments such as pharmacological pain relief, walking aids and passive treatments (e.g. manual therapy, acupuncture and other treatments given by a therapist and not requiring an active lifestyle change). Finally, third line treatments are only relevant for a few and include surgery, such as knee joint replacement surgery [3].

Pharmacological pain relief for management of knee OA

Despite pharmacological treatment being recommended as second line treatment, both over-the-counter and prescribed pain-relieving pharmacological agents (analgesics and anti-inflammatory drugs) are more widely and commonly used than first line treatment for knee OA treatment in primary health care [21]. While pharmacological agents are preferred for their ease of application and dose-dependent pain-relieving effect [22], they also have dose-dependent adverse effects [23-25].

Exercise therapy for management of knee OA

Exercise is an efficient treatment to reduce knee pain and improve function and quality of life in patients with knee OA [26-29]. The mechanisms by which pain is reduced through exercise are poorly understood and a variety of mechanisms have been described: neuromuscular components, peri-articular components, intra-articular components, general fitness and health components, and psychosocial components [30]. A variety of exercise interventions (i.e. aerobic exercise, isolated resistance training of the quadriceps muscle or lower limb, and performance exercise) have been used to treat knee OA [29, 31].

Neuromuscular exercise (NEMEX)

A major goal of traditional knee OA rehabilitation is to enhance muscle strength [32, 33]. The aim of NEMEX programs is different since the intention is to improve postural control (i.e. position of the trunk and lower limbs relative to one another) and functional performance (i.e. quality of movement performance) by challenging lower-limb muscles in functional positions [34].

Unlike conventional strength training, neuromuscular exercise addresses the quality of movement and emphasizes joint control in all three biomechanical/movement planes. Neuromuscular exercise has effects on knee functional performance, knee biomechanics and muscle activation patterns of the surrounding knee musculature. Neuromuscular exercise is used effectively for prevention and rehabilitation of anterior cruciate ligament injury [35-38], rehabilitation in patients with a meniscal tear with or without the combination of meniscectomy [1, 39] and in patients with moderate to severe OA prior to total joint replacement [40-42].

Theoretical framework

Introduction to knee biomechanics

The primary movement (i.e. flexion/extension) of the knee occurs in the sagittal plane (Figure 2A). With increasing knee OA severity, movements and/or malalignment (i.e. adduction/abduction or varus/valgus) of the knee in the frontal plane can develop (Figure 2B) [43], whereas alterations to movements (i.e. internal/external-rotation) in the transversal plane are more pronounced in ACL-deficient knees (Figure 2C) [44].

Moments such as the external knee adduction moment is the product of the moment lever arm and magnitude of the ground reaction force (Figure 2D), and can thus be altered by the magnitude/length of the lever arm or the magnitude/length of the ground reaction force.

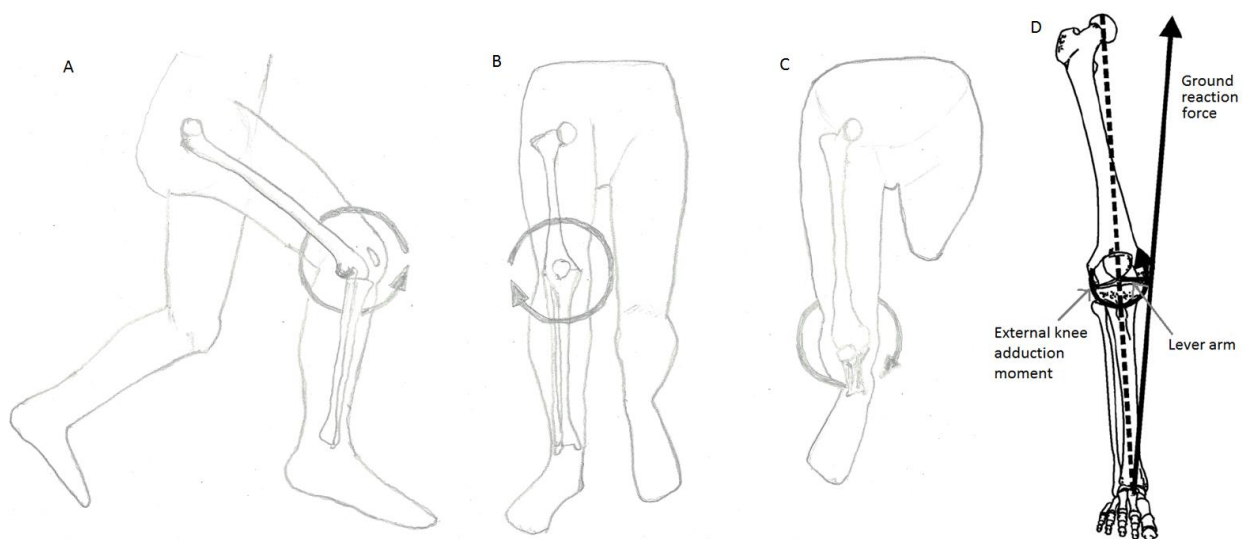


Figure 2: Planes and moments of the knee (A) sagittal plane, (B) frontal plane, (C) transversal plane, and (D) frontal plane moment lever arm and ground reaction force. Figure 2D, adapted from Münderman et al. [45].

This thesis is positioned within the framework of the following four interactions (Figure 3) [5]: 1) external measured knee loads during gait (Figure 3A) are related to the 2) internal knee joint forces acting on the knee (Figure 3B), which are the sum of muscle forces, passive tissue forces, and contact forces; 3) these internal forces determine cartilage tissue stress (Figure 3C); 4) which determine the cartilage metabolism (Figure 3D), that again can cause alterations in gait.

Specifically, this thesis will describe and analyze a novel load measure of total knee joint load and load modifying interventions (Figures 3A and B).

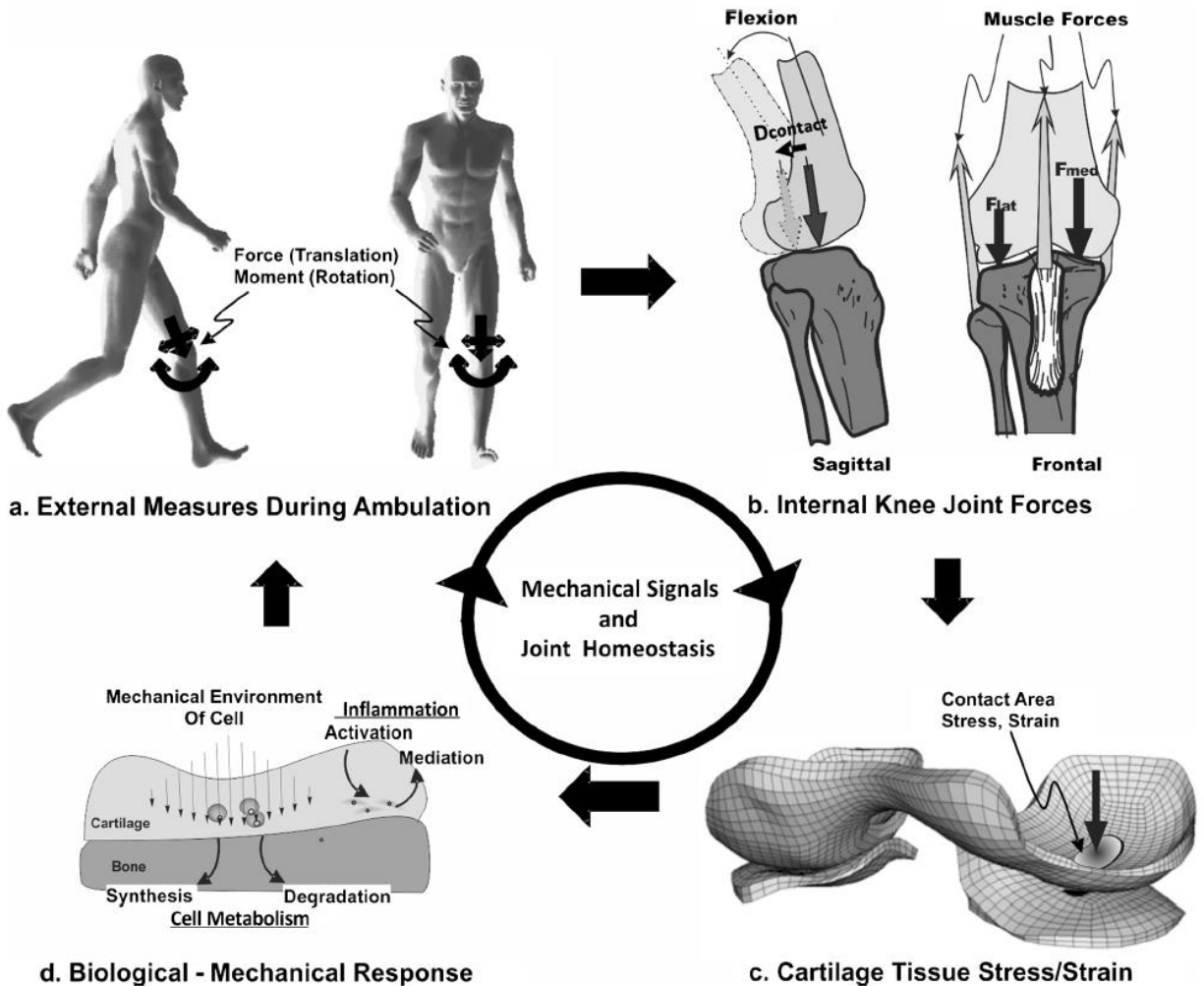


Figure 3: A conceptual model for biomechanical factors driving knee OA, (A) the external kinematic and kinetic signals related to knee OA, (B) the joint internal forces acting at the knee joint, (C) the cartilage tissue stress/strain is determined by internal force acting over an area of contact, and (D) the biological response is related to the local mechanical environment [5].

The role of external load on knee OA

Biomechanical factors are a driving factor for progression

During the stance phase of walking, relatively high loads are applied to the knee and loading of the medial knee compartment especially [46] has been associated with disease progression [47, 48], severity [49] and structural changes [50] in patients with knee OA.

Aetiology

The onset [5, 43] and progression [5, 51] of knee OA is to a large extent based on mechanical factors, that is, excess joint load or abnormal knee joint load or a combination of both. Excess knee joint load can be caused by an acute overload trauma (e.g. ACL rupture [52]), chronically with obesity [53, 54] or structural degeneration related to knee OA causing meniscal tears and malalignment [43]. Abnormal knee joint loads caused by abnormal anatomy of either congenital or acquired origin (e.g. partial meniscectomy [55]) can lead to increased focal stress on a certain part of the joint.

External knee loads relation to internal knee joint forces

External knee moments are used as a surrogate measure of compressive internal knee joint force. This assumption has been well established in approximately 10 subjects with load cell instrumented knee implants [46, 56-58]. Despite large variations in correlations ($R^2 = 0.44$ to 0.81), the relationship between the external knee adduction moment (KAM) and compressive medial knee joint force is considered robust at a group level but to a less degree at an individual level [46, 56-58]. KAM is, therefore, considered a valid outcome in OA research. It is important to note that subjects with instrumented knee implant [46, 56-58] have total knee joint replacements and presumably severe knee OA, and as a result, these findings might not be applicable to subjects with mild to moderate knee OA. However, two studies combining KAM and knee flexion moment (KFM) have improved correlation (from $R^2 = 0.63-0.87$ to $0.85-0.91$) between external moments and compressive medial knee joint forces, measured and estimated respectively in subjects with total knee joint replacement and ACL reconstruction [57, 59]. Thus, combining moments from more than one plane might lead to better estimates of compressive internal knee joint force.

Knee OA severity and variations in knee loads

Several cross-sectional studies have reported a relationship between radiographic knee OA severity and external peak KAM (Figure 4) [49, 60-65]. However, there does not seem to be a relationship between knee OA severity and peak KFM (Figure 5) [64-66]. Since the combination of KAM and KFM is better correlated to compressive medial knee joint forces than KAM or KFM alone, the combination is likely to be better related to knee OA severity.

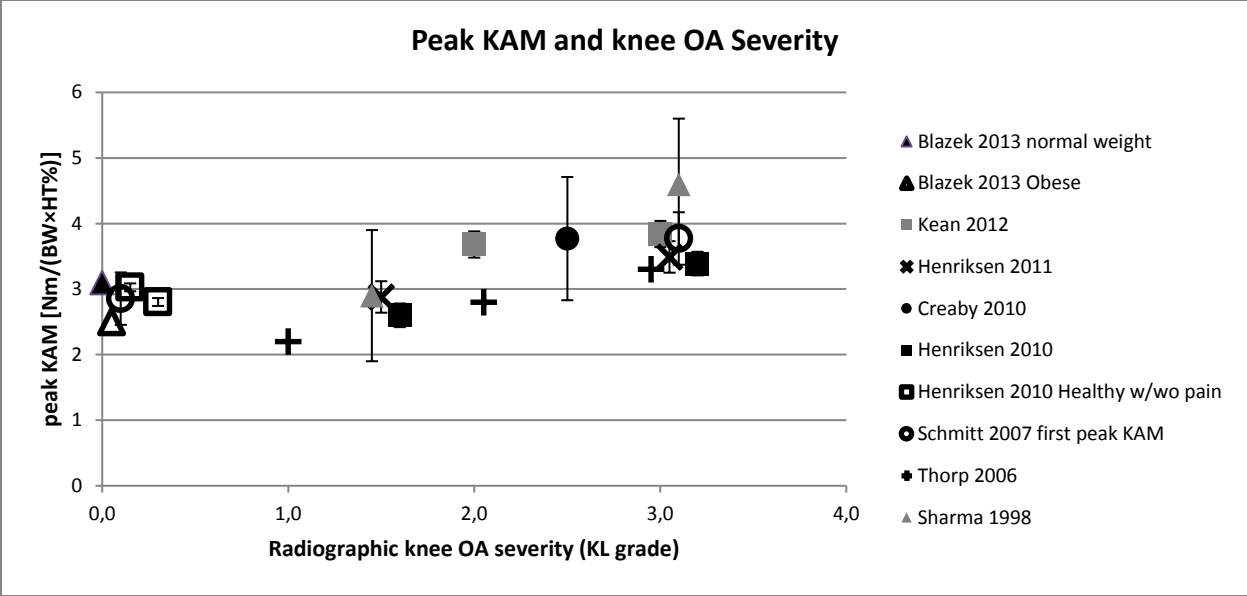


Figure 4: Relationship between external knee adduction moment and radiographic severity (KL grade), whiskers represents standard deviation (SD).

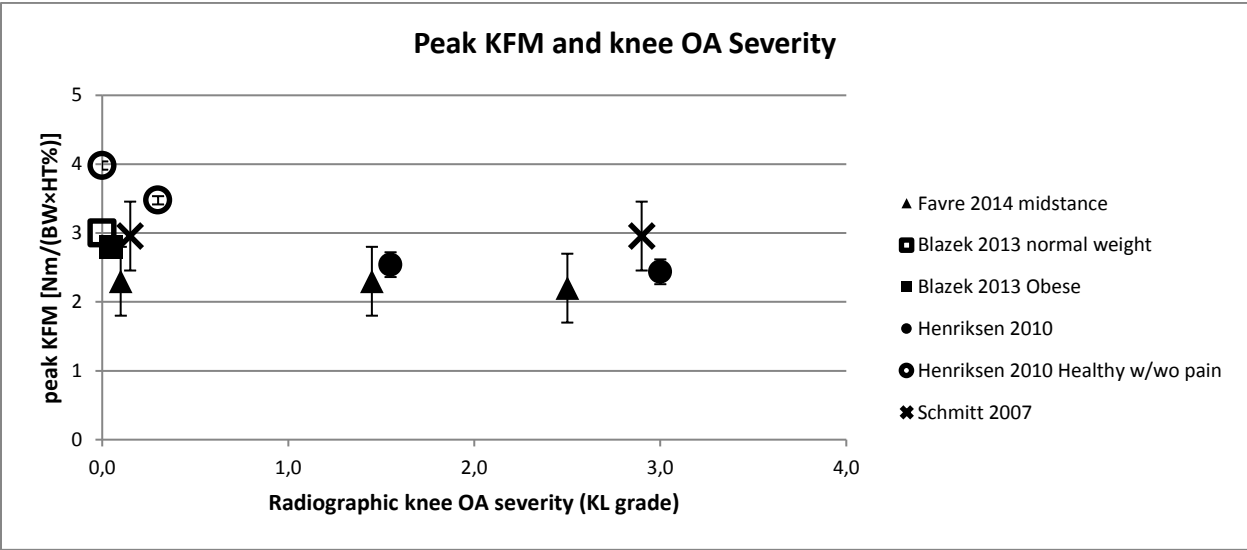


Figure 5: Relationship between external Knee Flexion Moment and radiographic severity (KL grade), whiskers represents standard deviation (SD).

A recent meta-analysis found very low evidence for a causal link between the external KAM and structural progression of knee OA in subjects with moderate to severe knee OA [67]. Although unknown, hypothetically it is more likely that the combination of KAM and KFM will show a causal link to knee OA progression.

Using outcomes composed of one plane only, such as KAM or KFM, may not provide the best assumption of medial compartment loading [68]. Thus, biomechanical outcome measures of total knee loading incorporating all three planes (frontal, sagittal and transversal) may be beneficial in OA research.

Development of a novel knee joint load measure

A novel knee joint load measure, the Knee Index (also described in the literature as ‘total reaction moment’ [69]), which includes moments from all three planes, has recently been introduced as a surrogate measure of total load across both knee compartments [69]. In contrast to KAM, the Knee Index is sufficiently sensitive to distinguish between pain relief induced by placebo, non-steroidal anti-inflammatory drugs (NSAIDs) or opioids in subjects with moderate knee OA [69]. Furthermore, external peak KAM has been shown to increase with age and knee OA severity [49, 60-63, 65], and no relationship between peak KFM and age has been found [64-66, 69]. This indicates that middle-aged individuals with mild to moderate knee OA use a knee-loading strategy composed of both KAM and KFM compared to older individuals with more severe knee OA. This further indicates that changes in KAM relate to changes in knee joint load to a limited degree only in middle-aged individuals with mild to moderate knee OA.

The Knee Index is a functional variable, constructed from the maximal external moments affecting the knee in the frontal, sagittal and transversal planes [70]. Although unknown, it is likely that subjects with knee OA develop individual loading strategies to manage pain and OA severity during gait. These strategies might vary from primarily loading the knee through the sagittal, primarily through the frontal plane or a relatively equal distribution through both planes. Such a hypothesized inter-subject variation in loading strategy will impact the utility of single-plane variables (e.g. KAM and KFM) in research and clinical practice to a greater extent than multi-plane variables (e.g. the Knee Index).

Thus, to interpret the underlying biomechanical characteristics of the Knee Index, the respective contributions of the knee moments derived from the three planes and potential inter-subject variation during gait are important to determine. Furthermore, overall knee joint load has been shown to be associated with altered gait strategies in the form of variation in single plane biomechanical variables (such as KAM, KFM, knee flexion/extension angle, knee alignment, etc.) [48, 71-75]. Thus, to determine if the Knee Index might be sensitive and responsive, it is important to determine associations between the Knee Index and a variety of single-plane measures in a case mix of individuals with mild to moderate knee OA. Considering the varied relationship between radiographic severity and KAM and KFM (Figures 4 and 5) [49, 60-66], it is important to determine if such a relationship also exists between the Knee Index and radiographic severity in individuals with mild to moderate knee OA.

The Knee Index is theoretically influenced by the functional alignment of the trunk, pelvis, and lower limb segments with respect to the knee *during movement* and the ground reaction force generated. Thus, it is likely that interventions, such as neuromuscular exercise, targeting the *efficiency* of lower limb movement and muscle activation patterns can be effective in improving dynamic knee joint loading [51, 76].

Neuromuscular exercise (NEMEX) and knee biomechanics

Subjects with degenerative knees are known to have deficiencies of sensory dysfunction, lower limb muscle weakness, altered muscle activation patterns and reduced functional performance [77]. NEMEX has been applied and has been shown to improve patient-reported outcomes, functional performance and knee extensor strength in subjects with risk of knee OA [39] and with severe knee OA [40, 78, 79]. Additionally, neuromuscular exercise increases functional knee stability and in pilot studies has shown potential to reduce knee joint loads and improve cartilage matrix quality in those at risk of, or with, mild OA [26, 27, 80] but not in those with malaligned knees and moderate to severe knee OA [81].

NEMEX and knee joint load

Despite its use in other conditions and in more severe stages of knee OA, there is only one study that has investigated the load-modifying effect of NEMEX in the early stages of knee OA. It was an uncontrolled pilot study consisting of 13 patients with mild knee OA [26]. This study found a -0.8Nm/kg (95% CI $-0.04;-0.16$) reduction (14%) in peak KAM during one-leg rise from a stool following 8 weeks of neuromuscular exercise. However, a randomized controlled trial showed no between-group difference in KAM comparing NEMEX and quadriceps exercise for subjects with severe knee

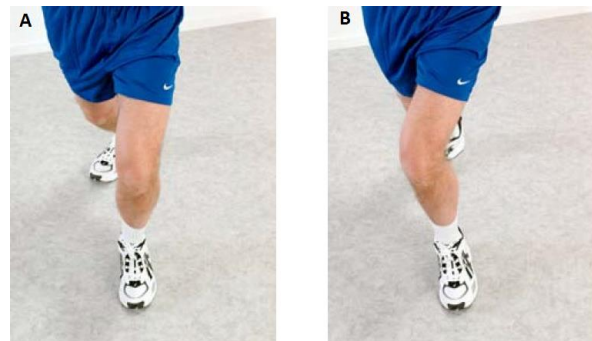


Figure 6: Correct (A) functional alignment 'Knee over foot position', and incorrect (B) functional alignment 'Knee medial to foot position' [1, 2].

OA and malalignment [79]. Despite conflicting results about disease severity, we hypothesize that NEMEX can amend knee joint load in individuals with mild to moderate knee OA. NEMEX can amend knee joint load in both the frontal and sagittal planes by improving alignment of the lower extremity (Figure 6A and B) and reducing functional instability [34], by improving muscle activation patterns of the surrounding knee musculature. Although unknown, we expect that NEMEX can reduce the overall knee joint load (Knee Index). The load in the frontal plane (KAM) can be reduced by improving functional knee alignment, thus reducing the ground reaction force-to-knee lever arm [82, 83], secondly the ground reaction force-to-knee lever arm can be altered by normalising foot progression angle (toe-in) and this can increase 1st peak KAM but reduce 2nd peak KAM [74, 83, 84], and normalised trunk lean (not leaning over weight bearing leg) can increase KAM [73, 83, 84]. The load in the sagittal plane (KFM) can be altered by NEMEX, firstly, by reducing gait speed and thereby the ground reaction force, and secondly, by reducing the knee flexion angle and thereby a decrease in KFM by reducing the ground reaction force-to-knee lever arm [85] and normalising the foot progression angle [74]. The transversal plane can be altered by NEMEX via improved functional knee alignment and functional stability, although the transversal plane is likely to play a limited role in the composition of the Knee Index due to its limited magnitude. In summary, NEMEX will be able to reduce 1st peak KAM and KFM by reducing the ground reaction force-to-knee lever arm and the ground reaction force by reducing gait speed. It is however, unknown if either KAM or KFM will be reduced equally, and if they are not, this may alter walking strategy.

Pharmacological pain relief and joint load in knee OA

Pain is a mechanism that helps to protect damaged tissue and tissue at risk of damage. In healthy subjects, experimentally induced knee pain has been shown to replicate altered gait movement strategies seen in patients with mild knee OA, that is, reduced 1st peak KAM and KFM [86]. The most common pharmacological pain relief used in the management of knee OA is acetaminophen and NSAIDs. Studies have shown that orally administered pharmacologically-initiated pain relief (acetaminophen and NSAIDs) in moderate knee OA is associated with increased loads in KAM (4% to 11%) and KFM (10% to 25%) (Figure 7) [69, 87, 88]. However, treatment also resulted in increased gait speed (7% to 16%) [69, 87], and it is possible that the increased knee loads reported are an effect of increased gait speed [72].

Additionally, studies of stronger pharmacological pain relief, injections with lidocaine or hyaluronic-acid, have been linked to increased 1st peak KAM, reduced KFM and increased gait speed [36, 89, 90] and Tanezumab® (nerve growth factor inhibitor) has been linked to knee OA progression [91, 92]. Therefore, pharmacological pain relief, by eliminating the protective mechanism of the pain itself, may be detrimental for knee joint structures by increasing overall knee joint load and thus we investigated this by use of the Knee Index.

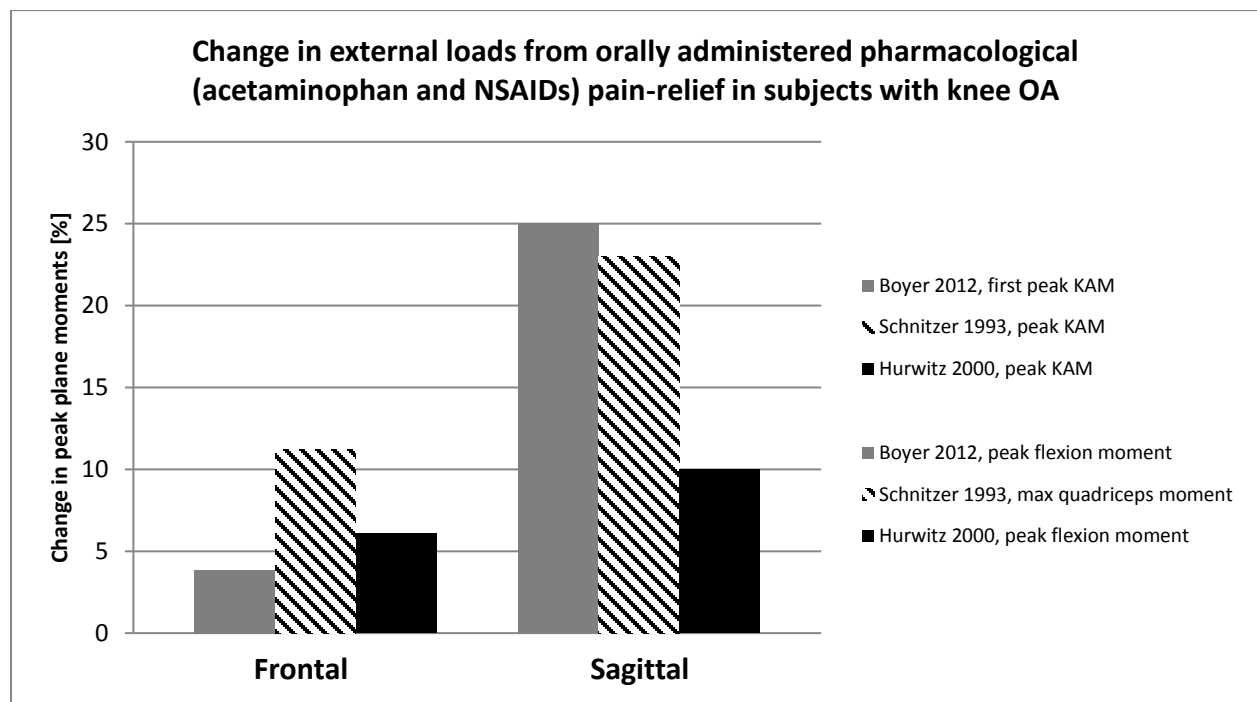


Figure 7: Change in external loads from pharmacological (oral NSAIDs) pain relief in subjects with knee OA. Changes seen for Hurwitz et al. are based on estimates. An increase in gait speed from baseline to follow-up, 6.6% and 16.3% was seen for Boyer et al. and Schnitzer et al., respectively.

Two pain relieving treatments

Multiple meta-analyses have shown that the pain-relieving effect seen from acetaminophen and NSAIDs is comparable with that of exercise [29, 31, 93-95]. Together with the previously described link between pharmacological pain relief and increased knee joint loads, it is likely that these two equally effective treatment modalities will affect the knee joint load in opposite directions [32, 47, 69, 96, 97].

Aims

General aims

The overall aim of this thesis was to compare the effectiveness of a specific neuromuscular exercise program with optimized analgesics and anti-inflammatory drug use on knee joint loads, as well as pain and functional performance in individuals with mild to moderate medial tibiofemoral knee OA.

Specific aims

The specific aims of this thesis were:

- To describe a novel biomechanical index of total knee joint loading in patients with mild to moderate knee OA by investigating: i) the relative contribution and inter-subject variation of each plane to the Knee Index and ii) how other biomechanical variables and radiographic severity relates to the Knee Index (paper I);
- To provide a detailed description of a progressive NEMEX therapy program aimed at improving postural control and functional performance in middle-aged subjects with mild to moderate knee OA, and to investigate the subjects' response to the program in terms of: i) progression over time in each exercise, ii) exertion after individual sessions, iii) pain, iv) adverse events, and v) adherence to training (paper II);
- To describe the protocol for a randomized controlled trial designed to compare the effectiveness of a specific neuromuscular exercise program with optimized analgesics and anti-inflammatory drug use on knee loads, as well as pain and functional performance in individuals with mild to moderate medial tibiofemoral knee OA (paper III); and
- To compare the effectiveness of a specific neuromuscular exercise program with optimized analgesics and anti-inflammatory drug use on knee loads (the 1st peak Knee Index), as well as pain and functional performance in individuals with mild to moderate medial tibiofemoral knee OA (paper IV).

Material and methods

All subjects involved in this thesis were allocated through the recruitment process of the EXERPHARMA trial (papers III and IV).

The EXERPHARMA trial has been approved by the regional Committee for Medical Research Ethics, Project-ID: S-20110153 and the Danish Data Protecting Agency. The study is registered at ClinicalTrials.gov, Identifier: NCT01638962. The Danish Medicines Agency has reviewed the protocol. The procedures followed are in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2000. Because the intervention involves advice on optimal use of analgesics instead of a prescription of a specified dose, the study is considered a non-pharmacological study and is therefore not required to undergo review by the Danish Medicines Agency's external trial unit.

Subjects

A sample of 93 subjects with knee OA (including both men and women) aged 40-70 years was recruited via primary care general practitioners (GPs) [98] in the community of Odense and Middelfart, Denmark, and from advertisements in local clubs, libraries, print media, and Facebook, from July 2012 to May 2015 (Figure 8). For a full list of inclusion and exclusion criteria, see Table 2. In summary, the eligibility criteria were selected to achieve high external validity of the study findings using a pragmatic trial design [99]. Patients had to have persistent knee pain in accordance with the ACR criteria [11] and no contra-indication for exercise, NSAIDs or x-ray, or have had leg surgery/trauma within the previous 6 months.

At the clinical examination, the subjects answered a questionnaire to record gender, age, weight, height, level of education, as well as working, smoking and civil status.

In Paper I, we used a cross-sectional design and we reported on baseline data from the EXERPHARMA trial, from the first 44 subjects who were included in the study from September 2012 to April 2014 (Figure 8).

In paper II, we used a case-series design and reported on the first 23 subjects (12 females and 11 males), randomized to supervised exercise therapy lasting 8 weeks with two sessions weekly in the EXERPHARMA trial (Figure 8).

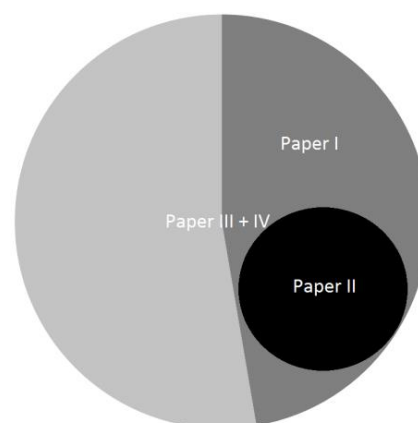


Figure 8: Subjects for this thesis. The large circle represents the total sample of 93 subjects in the EXERPHARMA trial (paper IV). The dark grey part represents the first 44 subjects included (paper I) and the black circle represents the first 23 subjects randomized to NEMEX-KOA (paper II).

Table 2: Eligibility criteria of the EXERPHARMA trial.

Inclusion criteria

1. Compliance with the ACR criteria:
 - a. Risk factors: Age >40years, female, overweight, occupation, family history of OA
 - b. Symptoms: Persistent knee pain, brief morning stiffness, functional limitations, acute knee pain
 - c. Objective examination: Crepitus during active movement, bony tenderness, bony enlargement, palpable effusion, no palpable warmth, restricted movement, joint instability
2. Medial knee OA of KL grades 0, 1, 2 and 3
3. Willingness to participate in exercise intervention and pharmacological intervention
4. A maximum of 80/100 points in the KOOS Pain subscale
5. BMI of less than 32

Exclusion criteria

1. General:
 - Difficulty complying with treatment schedule; inability to fill out questionnaires; inability to ambulate without assistive device; problems affecting the lower extremity overriding the problems from the kneePhysician-determined:
 - Any condition that is contraindicating use of acetaminophen, NSAIDs or exercise; already taking NSAIDs or acetaminophen at doses similar to or higher than the study dose; diagnosis of systemic arthritis
 2. X-ray:
 - Medial greater than lateral joint space width; medial knee OA of KL grade 4
 3. Surgical intervention:
 - At any point in the past:
 - ACL reconstruction; tibial osteotomy; ankle, knee or hip total joint replacement
 - Within the past 6 months:
 - Knee surgery including arthroscopy; steroid injection; known ACL deficiency
 - Within the next 6 months:
 - Knee surgery planned
-

Sample size calculation

In the EXERPHARMA trial (papers III and IV), the sample size calculation was based on the assumed superiority of the exercise intervention. For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05, we assumed a common standard deviation of Knee Index of 0.8 Nm/BW×HT% [69], and therefore a sample size of 42 subjects per group was required to obtain a power of at least 80% to detect a difference between the means of 1st peak Knee Index of 0.5 Nm/BW×HT% (corresponding to a 27% difference in means) [69]. To allow for some attrition during the trial period, we decided to include 100 subjects in total (randomized 1:1). If the drop-out rate proved to be lower, the number of recruited subjects was adjusted accordingly, but would not be below 84.

The EXERPHARMA trial (papers III and IV)

Trial design and setting

The EXERPHARMA trial (papers III and IV) was a single center, unstratified (with balanced randomization [1:1]), single-blind, controlled, parallel-group study conducted in Denmark. The study protocol conformed to the SPIRIT Statement [100] and the subsequent reporting followed the recommendations from the CONSORT Statement for non-pharmacological studies [101] (Figure 9).

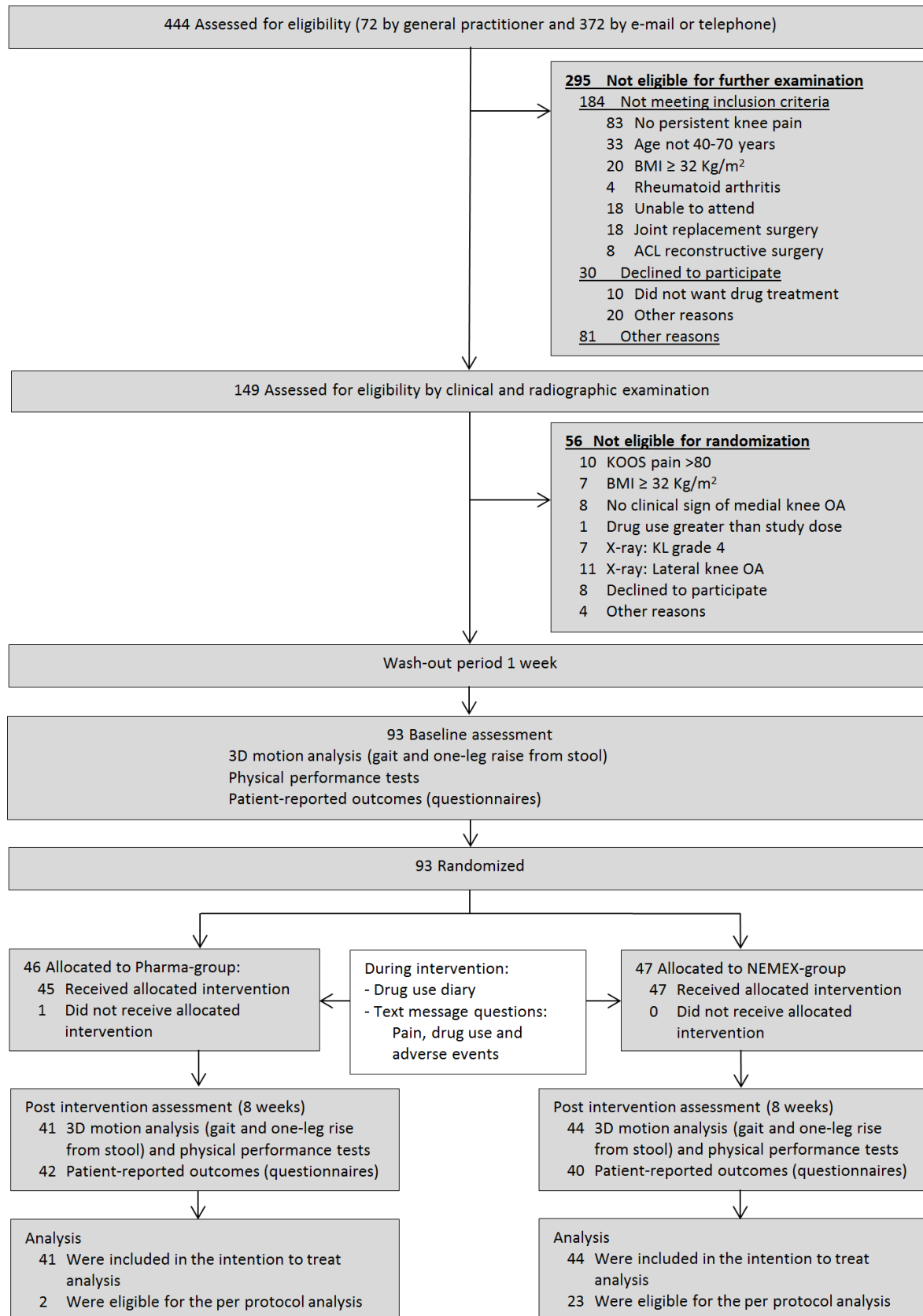


Figure 9: Flow diagram for the EXERPHARMA trial.

Procedure, randomization and allocation concealment and blinding (papers I to IV)

Subjects were given a short introduction to the study and were assessed for eligibility by a GP. The GPs were recruited via a letter of invitation and given an honorarium (the equivalent of €35) for each included subject. Subjects recruited through advertisements were assessed for eligibility by a physiotherapist. Thereafter, the subject was invited to a formal information meeting with the project manager, during which the signing of an informed consent form and a clinical assessment took place for every subject.

Eligible subjects were randomly allocated in permuted blocks of 4-6 generated *a priori* by our statistician to either the group receiving the NEMEX therapy (NEMEX-group) or the group receiving the analgesics and NSAIDs therapy (Pharma-group). Consecutively numbered opaque envelopes were opened after the subject had been tested at baseline by the project manager. The subject was informed about the allocation shortly after baseline testing.

The neuromuscular exercise program (papers II, III and IV)

We have applied the principles of neuromuscular training previously described in detail (*The NEMEX-KOA (NEuroMuscular Exercise – Knee OsteoArthritis)* [102]. In brief, each exercise session consisted of: warming up, neuromuscular exercises and cooling down (Table 5).

The *warming up part* was performed at a ‘rather strenuous’ level on Borg’s category ratio (CR-10) scale graded 0 to 10, where 0 is ‘no exertion at all’ and 10 is ‘maximal exertion’ [103, 104]. The *neuromuscular exercise part* comprised 11 exercises (Table 5) with the following key elements: functional performance, postural control, lower extremity muscle strength, balance and functional stability of the trunk and knee [34]. To allow for progression, four levels of difficulty were available for each exercise (with the exception of kettlebell swing and cable/elastic band exercises that only had three levels each) (for examples of levels of difficulty, see Table 5). Progression was made when the subject and supervising physiotherapist deemed that an exercise was performed with good sensorimotor control and good quality of performance. The *cooling down* part included gait retraining and stretching exercises for the lower extremity (Table 5) [39, 41, 42].

Training took place in groups, at one of two clinics under the supervision of experienced physiotherapists specialized in the training of musculoskeletal disorders. All treating physiotherapists in this study received education in the exercise program and the study’s data registration process. New subjects continuously entered the training group, that is, the group held both novice subjects and those who had participated in a number of the training sessions and, thus, were more familiar with the training regime. The subjects were offered two supervised training sessions a week, each of 60 minutes, and the intervention period was 8 weeks (up to a maximum of 16 sessions) [29]. In order to enhance compliance with the program, the importance of adhering to the exercises so as to achieve a training effect was explained to the subjects.

Rescue medication in the NEMEX-group (papers III and IV). Although we did not recommend it, subjects were allowed over-the-counter and prescribed pharmacological pain relief as rescue medication. Use of rescue medicine was noted by the subjects in their individual drug use diaries.

Table 5: Content of the 8-weeks neuromuscular exercise program (NEMEX-KOA) regarding exercises, volume and progression (examples of low and high level of exercise difficulty).

	Volume	Low level of exercise difficulty	High level of exercise difficulty
Warming up	10 min		
Ergometer cycling, treadmill or stepping exercise			
Neuromuscular exercises with a focus on strength gain			
Lunge	2 x 12 repetitions	No requirements, arms can be used for balance	With upper body rotation in the crouch position
Squat	2 x 12 repetitions	No requirements, arms can be used for balance	Kettlebell held in front of chest
Step-up	2 x 12 repetitions	With one foot on bench. Step up and down with the other foot	Stand on one foot on bench, jump down and land on the same foot
Kettlebell swing	2 x 12 repetitions	Kettlebell is held in both hands	Kettlebell held in one hand
Neuromuscular exercises with a focus on functional performance			
Weight transfer	2 x 12 repetitions	With flexed knees, move body weight from side to side	With a kettlebell resting on each shoulder
Mini trampoline	2 x 12 repetitions	Move body weight from side to side	Jump on one leg
Cloth under foot	2 x 12 repetitions	With the non-weight bearing leg sliding in abduction	With the non-weight bearing leg sliding in large figure eights
Cable/elastic band exercise	2 x 12 repetitions	Standing with both knees fully extended	Standing on a soft surface e.g. exercise mat
Neuromuscular exercises with a focus on postural stability			
Side lying jumping jacks	2 x 12 repetitions	In side lying with weight on forearm and hip; raise and lower pelvis controlled and slowly.	With the hip lifted from the ground, perform a full abduction in topmost arm
Pelvic lift	2 x 12 repetitions	Both feet on exercise ball. Lift and lower pelvis	With one foot on ball and pelvis lifted, flex and extend the knee
Neuromuscular exercises where some levels contained jumps			
Limping cross, all levels	2 x 12 repetitions	Hop on one leg straight forward and back	Hop on one leg around in the cross, first one way then the other
Mini trampoline, all levels	See above		
Squat level 2 and 4	See above		
Step-up level 3-4	See above		
Weight transfer level 3	See above		
Cooling down	10 min		
Stretching exercises for the lower extremity muscles			
Gait retraining e.g. walking in various ways including backwards with emphasis on alignment			

Data collection related to the exercise program (paper II)

At every exercise session, the physiotherapist recorded in an exercise diary the level of difficulty that all specific exercises were performed at.

Exertion for every exercise session was recorded by the treating physiotherapist by asking the subject to rate their exertion on the CR-10.

Pain from exercise was defined by the change in pain from 'prior to' to 'after' each exercise session and was recorded by the treating physiotherapist by asking the subject to rate their pain on a modified visual analog scale (VAS), graded from 0 to 10, where 0 is 'no pain' and 10 is 'pain as bad it could be'. The scale was split into three sections, pain up to 2 was considered 'safe' and coloured green, between 2 and 5 was considered 'acceptable' and coloured yellow, and pain above 5 was considered 'avoid' and coloured red [41, 105]. Increase in resting pain compared to normal was accepted as long as the increase had subsided to normal resting pain level 24 hours after the exercise session [32, 41, 105]. Finally, resting pain over the duration of the study was calculated as the change in resting pain from 'prior to' the first to 'prior to' the last exercise session.

Adherence to NEMEX-KOA for each subject was based upon attendance at the scheduled 16 sessions, and subjects exercising for less than 6 weeks (of the possible 8 weeks) were afterwards interviewed regarding reasons for low attendance.

Pharmacological pain relief (papers III and IV)

Subjects in the Pharma-group received information on how to best use mild analgesics (acetaminophen) and anti-inflammatory drugs (oral NSAIDs), in doses consistent with Danish guidelines [18]. Information was provided by a pamphlet and a video outlining their recommended use. The Osteoarthritis Research Society International (OARSI), the EULAR, and the Danish guidelines recommend starting treatment with acetaminophen up to 4g/daily in 3-4 doses. If acetaminophen proved to be inadequate, the treatment could be supplemented with an oral NSAID [18-20]. For subjects with an increased risk of gastrointestinal problems, a mucosal protector was recommended in addition to the NSAID. Subjects were encouraged to take their medication according to need, and they could change their medication when their pain level altered.

Treatment in the Pharma-group was designed to reflect recommended use of acetaminophen and over-the-counter NSAIDs. Therefore, subjects needed to pay for their own drugs. In Denmark, where the trial took place, the cost for full-dose (4,000mg daily for 8 weeks) use of acetaminophen would be the equivalent of €30 (in 2013 prices), and for full-dose (2,400mg daily for 6 weeks) NSAIDs (e.g. Ibuprofen) the cost would be the equivalent of €30. If subjects did not have sufficient pain relief from over-the-counter acetaminophen, the information pamphlet informed them to contact their GP, who may prescribe additional NSAIDs.

Outcomes

An overview of outcome measurements assessed in papers I-IV is presented in Table 3.

Table 3: Included outcome measures in paper I to IV. Only collection time point at 0 and 8 weeks will be presented in this thesis.

Outcome Measures	Collection time points	Paper I	Paper II	Paper III + IV
Biomechanical outcomes:				
Knee Index (primary outcome)	0, 8 weeks	•		•
1 st peak Knee Adduction Moment (KAM)	0, 8 weeks	•		•
Knee Adduction Moment (KAM) Impulse	0, 8 weeks			•
Other biomechanical variables	0, 8 weeks	•		
Physical performance:				
Functional performance tests	0, 8 weeks			•
Aerobic capacity	0, 8 weeks			•
Patient-reported outcomes:				
Knee injury Osteoarthritis Outcome Score (KOOS)	0, 8, 52 weeks	•	•	•
Activity level	0, 8, 52 weeks		•	•
Pain level (text messages)	During treatment			•†
Adverse events (questionnaire)	0, 8 weeks		•§	•
Adverse events (text messages)	During treatment			•‡
Drug use (diary: amount, intensity and type)	During treatment			•
Drug use (text message)	During treatment			•†
General health measure	0, 8, 52 weeks			•†
Health economic evaluation	0, 8, 52 weeks			•†
Pain 'prior to' and 'after' exercise	During treatment		•	
Exertion in exercise group	During treatment		•	
Observer-reported outcomes:				
Performance in exercise group	During treatment		•	
Structural outcomes:				
Radiographic severity	0, 8 weeks	•		•†

§ Adverse events were restricted to the musculoskeletal system.

† Outcomes are reported in the paper, and not in this thesis.

‡ Outcomes are planned to be reported in future publications.

Biomechanical outcomes

All biomechanical outcome calculations were based upon measurements taken of the study knee during gait before and after treatment using a 3D Vicon MX movement analysis system with eight cameras operating at 100 Hz (Vicon, Oxford, UK) and two AMTI force-plates (AMTI, OR6-7, Watertown, MA, USA) embedded at floor level, operating at 1000Hz. Due to hardware upgrade during the inclusion period, the first 24 subjects were measured with a 3D Vicon MX movement analysis system with six cameras operating at 100Hz (Vicon, Oxford, UK) at both baseline and post intervention. A technician experienced in gait analysis and the Vicon system placed reflective markers that reflect near-infrared light according to the Vicon Plug-in-Gait marker set and model [106, 107]. Data were combined using inverse dynamics to yield measures of external joint moments and ranges of motion and calculated by Plug-In Gait software. Subjects were instructed to walk at their preferred gait speed at baseline and follow-up. If gait speed at follow-up deviated more than $\pm 5\%$ from baseline, subjects were asked to either walk faster or slower. The overall agreement and reliability in our laboratory corresponds to a minimal detectable

change (MDC) of 19.3% and 26.7%, and intraclass correlation coefficients of 0.81 and 0.76 for Knee Index and first peak KAM respectively.

The Knee Index – primary outcome of the randomized controlled trial (papers I, III and IV)

The primary outcome for the EXERPHARMA trial was change in knee load in the study knee during gait. The primary outcome was between-group change in the Knee Index immediately after intervention. External peak joint moments in the frontal, sagittal and transversal planes of the first 10-50% of the stance phase were used to calculate the Knee Index (Figure 10) [70]. The Knee Index is a surrogate for total load across both compartments, and has been chosen since changes in the external moment are known to occur in the sagittal plane prior to and without accompanying changes in the frontal and/or transversal plane [51, 69, 108]. The Knee Index will be reported normalized for height and weight.

$$Knee\ Index = \sqrt{\left(\frac{(Frontal\ plane\ moment^2 + Sagittal\ plane\ moment^2 + Transversal\ plane\ moment^2)}{3}\right)}$$

Figure 10: Equation for calculating the Knee Index.

In paper I, we investigated the properties of the Knee Index by determining the contribution from the three planes (frontal, sagittal, transversal) and the correlation between the Knee Index and other biomechanical outcomes.

Other biomechanical variables (paper I)

To investigate biomechanical variables that might relate to the Knee Index in this study, we tested a number of variables (see Table 4 for a detailed description of collection and calculation of each of them). These variables have previously been found to be related to the variability of knee joint load or disease severity: time point [71], dynamic sagittal plane angle [48, 71], knee alignment [71, 72, 109] and gait speed [72] Additionally, we included biomechanical variables that have been associated with alterations in gait strategies (i.e. trunk lean [73, 84] and foot progression angle [74, 75, 110]).

Additional biomechanical outcome for the EXERPHARMA trial (paper III and IV)

The secondary biomechanical outcome for the EXERPHARMA trial (Table 3) was 1st Peak KAM during gait normalized for height and weight. As explorative outcomes we chose KAM impulse normalized for height and weight, and gait velocity.

Table 4: Collection and calculation of biomechanical variables used in paper I.

Variable	Unit	Collection time point	Calculation
Knee Index	Nm/(BW×HT%)		Combined using inverse dynamics
1 st peak KAM	Nm/(BW×HT%)		Combined using inverse dynamics
Frontal plane moment	Nm	Knee Index	Combined using inverse dynamics
Sagittal plane moment	Nm	Knee Index	Combined using inverse dynamics
Transversal plane moment	Nm	Knee Index	Combined using inverse dynamics
Time point	% of stance phase	Knee Index	Recorded for each subject at every gait trial
Dynamic knee sagittal plane angle	°	Knee Index	Calculated angle between the hip and shank
Knee alignment			
Dynamic knee frontal plane angle	°	Knee Index	Calculated angle between the hip and shank
Static knee frontal plane angle	°	Standing in anatomical neutral position with feet symmetrical and comfortably apart	Extracted from commercial software Nexus 1.8.5 Standard static trial plug-in-gait procedure. Calculated angle between the hip and shank
Gait speed	m/s	Start to end of each gait trial	Calculated as the horizontal velocity of body center of mass.
Trunk lean			
Spine angle	°	Knee Index	Calculated relative to the pelvis
Thorax angle	°	Knee Index	Calculated relative to the lab.
Foot progression angle	°	Knee Index	Calculated relative to the lab.

Physical performance measures for the EXERPHARMA trial (papers III and IV)

To evaluate functional performance [111], we chose three tests that have shown evidence of validity in knee OA as secondary outcomes for the EXERPHARMA trial, in the following order: maximum number of one-leg rises from a stool [112], maximum number of knee-bends in 30s [113], and one-leg hop for distance [113]. To avoid systematic bias due to a potential learning effect, the leg to be tested first was randomized at the time of each testing [113].

Maximum one-leg rises from a stool. This test evaluates the number of times the subject can rise from a stool standing on one leg [26, 112, 114]. A lower number of one-leg rises has been found to be predictive of development of radiographic signs of OA [112]. The test was to be performed with full muscle control, that is, the sitting down phase should be performed at constant speed and the rising up phase was to be performed without adding arm or trunk movement. This test was recorded with 3D motion capture.

Maximum number of knee-bends performed in 30 seconds. This test evaluates the ability to perform fast changes between eccentric and concentric muscle force over the knee joint, and has been found to be reduced in subjects with and without radiographic knee OA at 20 years following meniscectomy compared to healthy controls [113, 115]. The subject stood on one leg with support provided by fingertips touching a custom made frame. The subject bends his/her knee, without bending forward from the hip, until approximately 30° of knee flexion consecutively for 30 seconds [113].

One-leg hop for distance. This test mimics sporting activities and demands explosive muscle function, balance and functional stability of the knee, and has been found feasible for subjects with radiographic knee OA [113, 116, 117]. The subject stood on the leg to be tested, hopped, and performed a controlled, balanced landing on the same leg. Shoes were worn.

Aerobic capacity measured with the Åstrand VO_2max test [104]. Prior to the 3D movement analysis and functional performance tests, subjects performed a standardized warm-up session consisting of the Åstrand VO_2max test. The subject cycled at 60 rpm, with the workload adjusted to target a stable heart rate of 120-170 bpm. From pulse rate and workload, the aerobic capacity was estimated. Change in Åstrand VO_2max was chosen as a 'not pre-specified outcome' for the EXERPHARMA trial.

Patient-reported outcomes

The Knee injury and Osteoarthritis Outcome Score (KOOS) (papers I to IV) [118-120] is a questionnaire that assesses self-reported outcomes in five separate subscales: Pain, Other symptoms, Activities of Daily Living (ADL), Sport and Recreation Function, and Knee-related Quality of Life (QOL), calculated as separate subscale scores ranging from 0 to 100, worst to best. Change in KOOS was chosen as a secondary outcome for the EXERPHARMA trial.

Activity level (papers II to IV) was assessed with the University of California at Los Angeles (UCLA) activity score [121]. It assesses self-reported current activity level on a scale of 1 to 10, worst to best. Change in UCLA was chosen as an explorative outcome for the EXERPHARMA trial.

General health (papers III and IV) was measured with the short form health survey (SF-36) [122] that is a generic measure of health status measuring physical and mental aspects in eight different subscales, calculated in separate subscale scores ranging from 0 to 100, worst to best. SF-36 was used to describe the study population at baseline for the EXERPHARMA trial and not reported in this thesis.

Health economic evaluation (papers III and IV). In order to be able to perform a health economic evaluation, the subjects completed the EuroQOL (EQ-5D). EQ-5D [123] is a utility index measuring the five dimensions of anxiety, mobility, self-care, pain and usual activities. It indicates the level of health-related quality of life for each EQ-5D health state, on a scale from 1 (full health) to 0 (dead) [range - 0.624 to 1, where negative values are valued as worse than dead] [124]. EQ-5D was used to describe the study population at baseline for the EXERPHARMA trial and not reported in this thesis.

Adverse events (papers II to IV). The reporting of adverse events was elicited with a non-leading questionnaire at baseline and after treatment. All events were coded according to the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products [125]. Change in adverse events was chosen as an explorative outcome for the EXERPHARMA trial.

Drug use (papers III and IV). In both treatment groups, subjects completed a 'drug use diary', in which they were asked to fill in date, time, type and amount of any given pain relieving drug they used each day during the treatment period. In addition, they could fill in the reason for taking the drug e.g. headache or knee pain. Drug use was also measured during treatment by text messages. Drug use measurements were chosen as explorative outcomes for the EXERPHARMA trial.

Text messages (papers III and IV). Pain was also measured during treatment by text messages. Both groups were contacted by Short Message Service (text messaging) on their mobile phone twice a week (in total, 16 assessments) and were asked to answer 3 questions: 1. "What is your level of pain right now?" (0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = extreme); 2. "Did you use any pain relieving drug yesterday?" (yes/no); 3. "Have you had any adverse event since the last text message?" (yes/no). If a subject answered yes to question 3, the subject was contacted by the project manager to identify the nature of the adverse event. Text messaging has been successfully used previously to evaluate real-time back pain [126]. Text messages were used to evaluate pain and drug use in the EXERPHARMA trial and not reported in this thesis. Text messages evaluating adverse events were not reported.

Structural outcomes (papers I, III and IV)

Radiographic severity (papers I to IV) was classified according to the Kellgren-Lawrence (KL) classification in grades 0-4, with grade 4 being an exclusion criterion. Grade 0 corresponds to 'no osteoarthritis', grade 1 to 'Doubtful narrowing of joint space or possible osteophytes', grade 2 to 'Definite osteophytes and possible narrowing of joint space', grade 3 to 'Multiple osteophytes, definite narrowing of joint space and some sclerosis and deformity of bone ends' and grade 4 to 'Large osteophyte, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends' [13, 14]. The KL grade was also used to investigate if radiographic severity relates to the Knee Index and knee-loading strategy (paper I). Plain radiographs of both knees were taken, in posterior-anterior and medio-lateral directions and patella skyline. The posterior-anterior radiographs were taken with the subject standing at a fixed flexion angle using the Synaflex® frame [127]. The medio-lateral radiographs were taken with the subject standing with semi-flexed knees ($\approx 10^\circ$) and the tibia kept vertical [128]. The patella skyline radiographs were taken with the subject standing with flexed knee ($\approx 70-110^\circ$) with the x-ray beam level with the base of the patella [128]. Radiographic severity was used to describe the study population at baseline for the EXERPHARMA trial and reported for paper I in this thesis.

Statistical analysis

Statistical methods for cross-sectional study (paper I)

Data were tested for their distribution by histograms, qq-plots and Shapiro-Wilks test and most were found to be normally distributed, or became normally distributed by logistic (ln) transformation, and subsequently parametric methods were applied. Five variables (sagittal plane moment, time point, static knee frontal plane angle, foot progression angle and KL grade) were analyzed with non-parametric methods. Data were analyzed in two steps: i) Inter-subject and within-subject variance of the composition of the Knee Index (see below), and ii) the sample was divided into two sub-groups according to composition of the Knee Index (knee-loading strategy) and the relation of other biomechanical variables to Knee Index was, for the whole sample and both sub-groups, analyzed by simple linear regression analysis (see below).

Variance of composition of Knee Index

The relative contribution from the frontal, sagittal and transversal plane knee moments to the Knee Index was calculated for all three planes of the study knee at the instant time points of the Knee Index (Figure 11). The inter-subject variability of the Knee Index was analyzed by calculating standard deviation and by visual inspection of the composition of the Knee Index.

$$\begin{aligned}\%Frontal &= \left(\frac{\left(\frac{Frontal\ plane\ moment^2}{Knee\ Index^2} \right)}{3} \right) * 100\% \\ \%Sagittal &= \left(\frac{\left(\frac{Sagittal\ plane\ moment^2}{Knee\ Index^2} \right)}{3} \right) * 100\% \\ \%Transversal &= \left(\frac{\left(\frac{Transversal\ plane\ moment^2}{Knee\ Index^2} \right)}{3} \right) * 100\%\end{aligned}$$

Figure 11: Equation for calculating contribution to Knee Index.

Regression and sub-group analyses (paper I)

Simple regression analysis was employed to assess the association of biomechanical variables with the Knee Index on all (n = 44) individuals. In addition, due to the findings of large inter-subject variation in the composition of the Knee Index (see results section), a post hoc decision was made to divide the sample into two sub-groups according to composition of the Knee Index: 1) one sub-group with a frontal knee-loading strategy, where the Knee Index was primarily composed of the frontal plane moment (>50%) (n = 22), and 2) one sub-group with a sagittal knee-loading strategy, where the Knee Index was primarily composed of the sagittal plane moment (>50%) (n = 22). The regression analyses were conducted using the Knee Index as the dependent variable and the other biomechanical variables and radiographic severity as the independent (explanatory) variables. For the regression analyses, based on Dancy and Reidy's categorization [129], we considered $R \geq 0.10$ as a low correlation, $R \geq 0.40$ as a moderate correlation and $R \geq 0.70$ as a high correlation.

Statistical methods for the EXERPHARMA trial (papers III and IV)

A complete study protocol [102] and a statistical analysis plan were published prior to analysis and unblinding of group allocation. The project statistician who performed all the analyses was masked to group allocation. Data were checked for completeness, and descriptive statistics were calculated for patient characteristics. Main comparative analyses between groups were performed on the full analysis set (i.e., the intention-to-treat population); missing data were imputed using baseline observation carried forward. Between-group mean differences were analyzed using a general linear model Analysis of Covariance (ANCOVA) techniques, with a fixed factor for group (2 levels) adjusted for baseline values [130].

To assess the adequacy of the linear models describing the observed data—and checking assumptions for the systematic and the random parts of the models—we investigated the model features via the predicted values and the residuals, that is, the residuals had to be normally distributed (around 0) and be independent of the predicted values.

Sensitivity analyses were performed to assess the robustness of the primary multiple-imputation analyses, which used model-based approaches for missing data. Also, we confirmed the robustness using analyses based on ‘as observed’ rather than the ITT principle. The SAS statistical package (V.9.4; SAS institute Inc, Cary, North Carolina, USA) was used for all statistical models. A two-sided P-value of 0.05 was used to provide evidence against the null hypothesis; i.e., results are expressed as estimates of the group differences in the changes from baseline, with 95% CIs to represent precision of the estimates.

Good compliance was defined *a priori*, in the NEMEX-group, as those subjects who participated in at least 12 exercise sessions, and in the Pharma-group, as those subjects who used pharmacological pain relief (acetaminophen or equivalent dose of NSAID) of more than 2,000 mg/daily on at least 28 days during intervention.

Data interpretation

To minimize bias, we decided *a priori* on how to interpret the possible variation in follow-up data scenarios: 1) if knee joint load were reduced more in the NEMEX-group compared to the Pharma-group, then NEMEX would be the preferred treatment; 2) if knee joint load were reduced more in the Pharma-group compared to the NEMEX-group, then Pharma would be the preferred treatment; 3) if knee joint load did not differ between the two treatment groups, the treatment associated with the greatest pain relief, functional improvement and the least adverse events would be favoured.

Summary of results

Subjects and compliance (paper IV)

In total, 72 individuals were initially assessed for eligibility by a GP and 372 by e-mail or telephone interview (Figure 9). Of these, 149 were assessed for eligibility by clinical and radiographic examinations. Ninety-three subjects (85% women, 58 ± 8 years with a BMI of 26.9 ± 3) were randomized to either the NEMEX-group ($n = 47$) (62% women, 58 ± 8 years with a BMI of 27 ± 3) or the Pharma-group ($n = 46$) (54% women, 58 ± 8 years with a BMI of 27 ± 3). Data from 44 and 41 patients, respectively, were available at follow-up (Figure 9). Of the 47 participants in the NEMEX-group, 23 (49%) fulfilled the pre-defined good compliance of ≥ 12 sessions. Only 3 (7%) subjects had good compliance with the drug treatment intervention (the Pharma-group), defined as taking at least 2,000 mg/daily of acetaminophen or equivalent dose of NSAID for at least 28 days. A similar intake of pain relievers were reported for both groups.

Development of a sensitive knee load index (paper I)

In the first 44 subjects included in the EXERPHARMA trial, the Knee Index was mainly composed of frontal ($53.5\% \pm 26.5$) (mean \pm SD) and sagittal plane moments ($46.1\% \pm 26.8$). The contribution from the transversal plane was minor ($0.4\% \pm 0.5$). Furthermore, a large inter-subject variation was found, expressed as large standard deviations (26.5-26.8) in the primary contributors to the Knee Index. The contribution of the frontal knee moment strategy, expressed as KAM, varied from 2.2% to 98.1% for the 44 individuals (Figure 12).

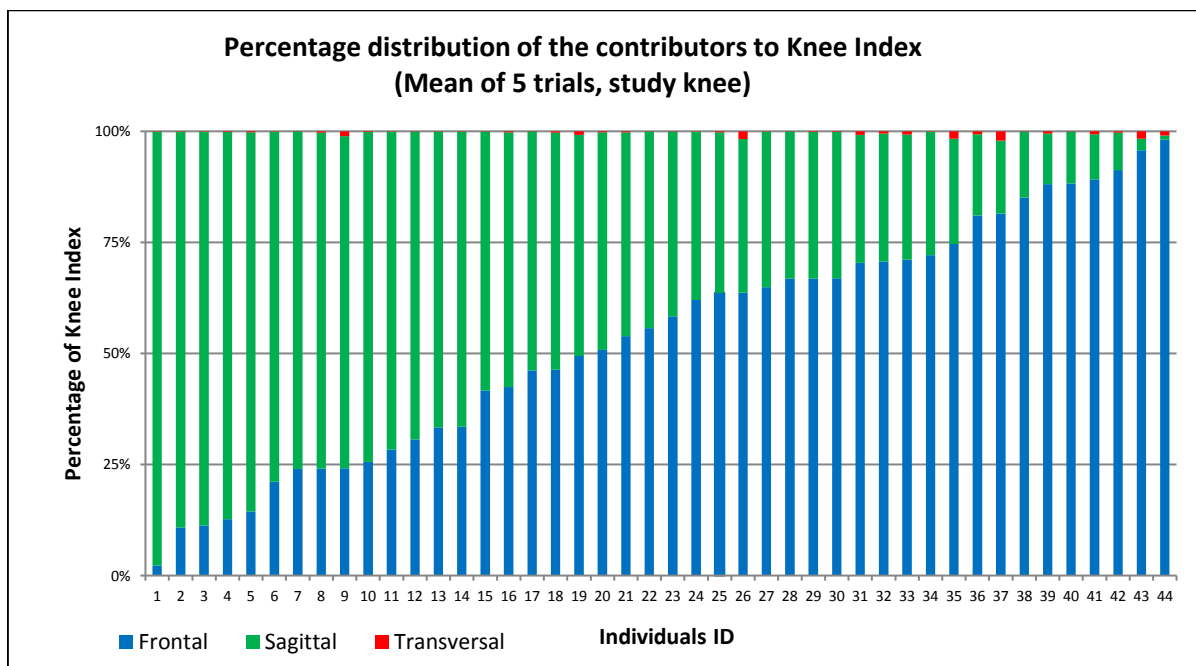


Figure 12: Individual variation - percentage distribution of the contributors to Knee Index (study knee) in the 44 individuals. Individuals are ordered from lowest to highest frontal plane contribution – Mean of 5 trials.

The total sample was divided into sub-groups based upon frontal or sagittal knee moment strategy. As shown in the time-course patterns for the whole sample (Figure 13A), the sagittal strategy sub-group is characterized with frontal plane moments close to zero for the first half of the stance phase (Figure 13B), whereas the frontal strategy sub-group is characterized with sagittal plane moments close to zero for the first half of the stance phase (Figure 13C), and the contribution from the transversal plane is very little in the whole sample and both sub-groups.

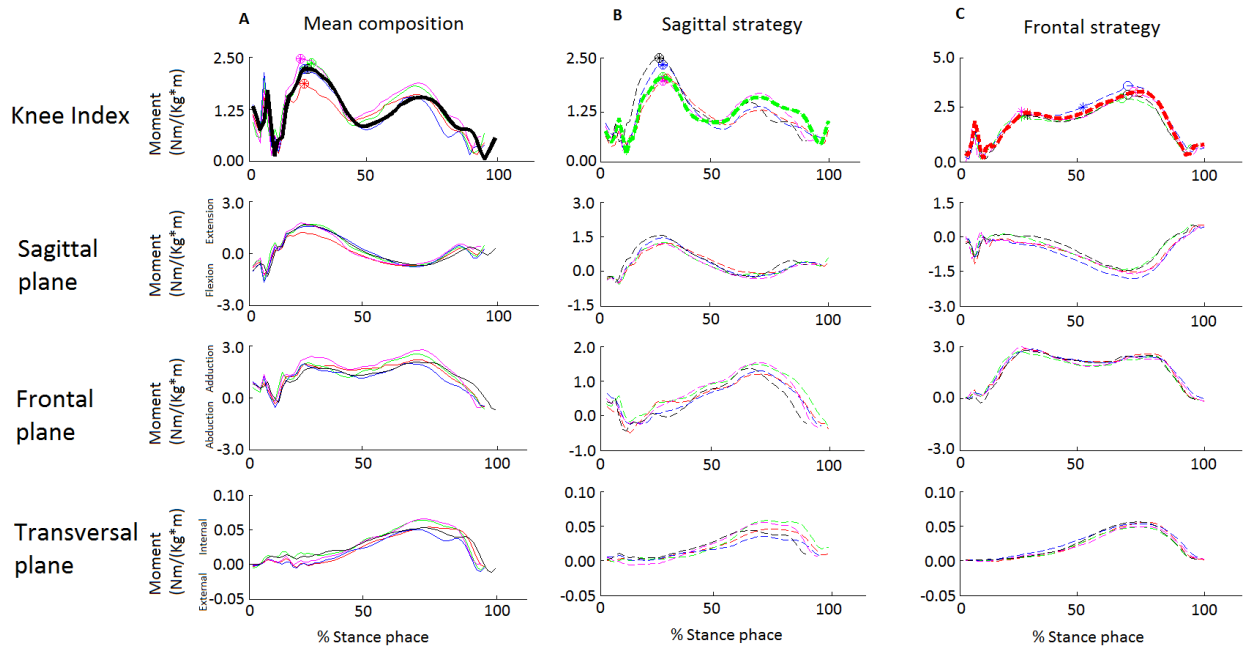


Figure 13: Examples of time-course patterns of the Knee Index, sagittal, frontal and transverse plane moment, according to different loading strategies. (A) Represents the mean of all subjects, (B) represents subjects with sagittal loading strategy, and (C) represents subjects with frontal loading strategy.

Association between Knee Index and other biomechanical variables

The sub-group analyses resulted in better associations (higher R-values) than the analyses conducted on all individuals. The sub-group with a frontal knee-loading strategy only showed associations between the Knee Index and frontal plane kinetics and kinematics, whereas the sub-group with a sagittal knee-loading strategy showed associations between the Knee Index and both frontal and sagittal plane kinetics and kinematics, and gait speed. Additionally, no associations were seen for variations in transversal plane and for variables representing altered gait strategies, trunk lean and foot progression angle. No association between the Knee Index and KL grade was seen for both the whole group and sub-groups.

Feasibility of NEMEX-KOA (paper II)

Progression of exercises

For the first 23 subjects randomized to NEMEX-KOA, it was possible for the 18 subjects who participated in six or more sessions to progress to the more complex levels of difficulty in half or more of the neuromuscular exercises, and overall, those subjects who performed a greater number of exercise sessions were able to progress to a higher level of difficulty. The neuromuscular exercises were grouped into four categories:

- *Neuromuscular exercises with a focus on strength gain* including the exercises: squat, lunge, step-up and kettlebell swing (Figures 14 A, B, C and D).
- *Neuromuscular exercises with a focus on functional performance* including the exercises: weight transfer, cloth under foot, mini trampoline and cable/elastic band (Figures 18 E, F, G and H).
- *Neuromuscular exercises with a focus on postural stability* including the exercises: pelvic lift and side lying jumping jack (Figures 14 I and J).
- *Neuromuscular exercises where some levels contained jumps* including: all levels of limping cross and mini trampoline, squat level 2 and 4, step-up level 3-4 and weight transfer level 3 (Figures 14 A, C, E, K and G). Less than half of the subjects were able to progress and perform exercise levels containing jumps with high impact on landing (Figures 14 A, C and K), when not performed on a trampoline or on a soft exercise mat (Figures 14 E and G).

Exertion and pain

Perceived exertion of the exercise program for the individual subjects ranged from 'light' to 'very heavy'. Overall, we found few reports of a clinically relevant increase in pain from exercise and few reports of high pain following exercise. Four of the 23 subjects reported a short-term clinically relevant increase in pain from exercise (defined as >2 VAS points) after 1-2 out of the 16 scheduled sessions. The increase in pain was temporary and subjects were able to continue the exercise program.

Adverse Events and adherence

None of the 23 subjects reported any treatment-specific musculoskeletal adverse events.

Seven of the 23 subjects attended exercise for less than 6 weeks, three of these stopped due to knee pain, and one specified that the pain was due to the original pain and disability and not necessarily aggravated by the exercise. The remaining four subjects who attended for less than 6 weeks had low attendance for other reasons, such as work commitments or transportation difficulties and, in one case, a cardiovascular procedure.

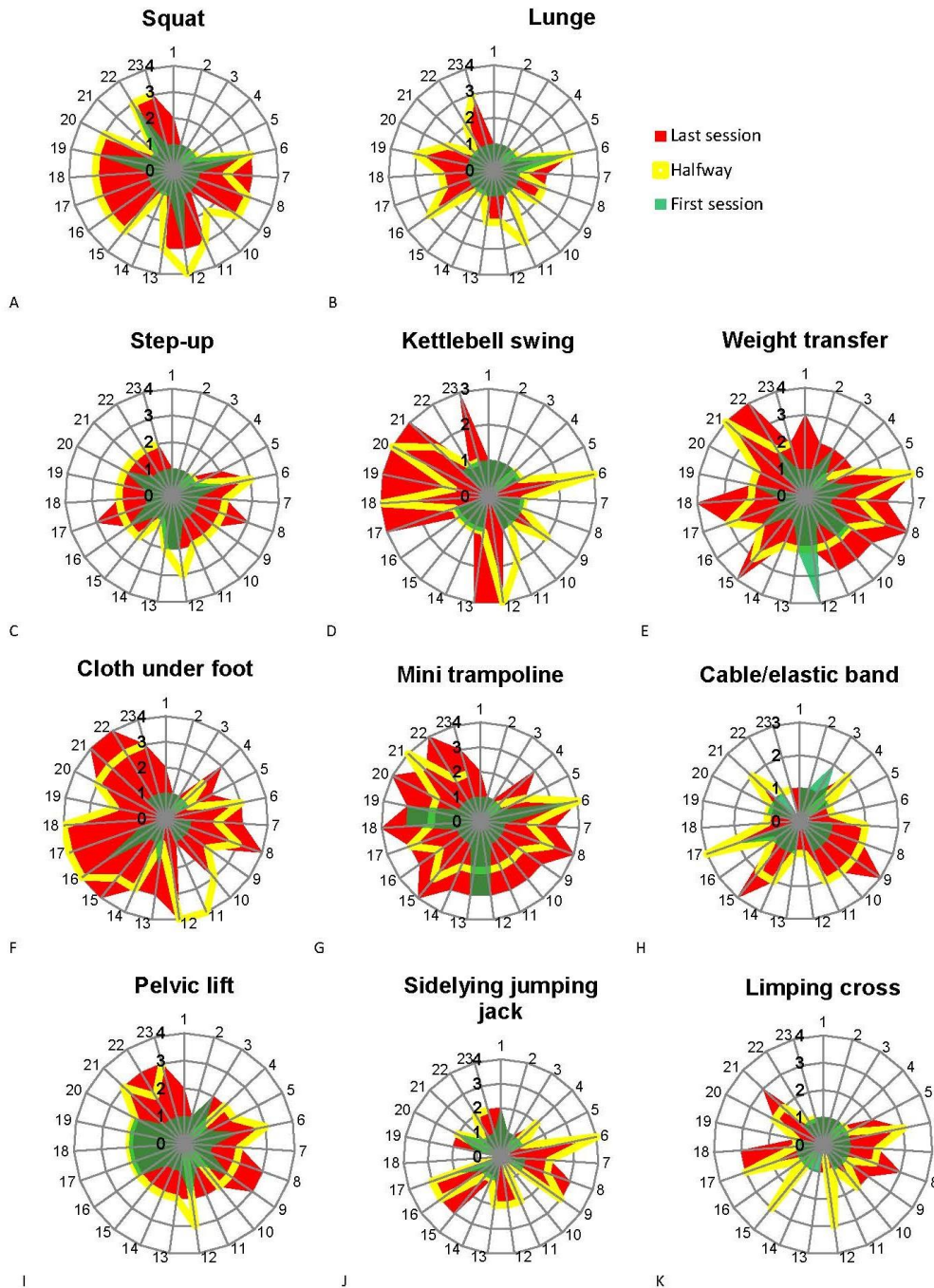


Figure 14: Level of difficulty at which each exercise was performed at the first, halfway and last exercise sessions. Neuromuscular exercises with a focus on strength gain ((A) squat, (B) lunge, (C) step-up and (D) kettlebell swing), exercises with a focus on functional performance ((E) weight transfer, (F) cloth under foot, (G) mini trampoline, (H) cable/elastic band), exercise with a focus on postural stability ((I) pelvic lift and (J) side lying jumping jacks) and exercise where some levels contained jumps ((G) mini trampoline, (K) limping cross, (A) squat level 2 and 4, (C) step-up level 3-4 and (E) weight transfer level 3). The numbers (0-3/4) from the center to the circumference correspond to level of difficulty, 1 being the lowest. The numbers (1-23) around the circumference refer to the 23 individual subjects. The green area indicates the level of difficulty for the individual 23 subjects at the first session. The yellow line indicates the level of difficulty for the individual 23 subjects at the halfway session. The red area indicates the level of difficulty for the 23 individual subjects at the last session. Subjects with identification (ID) 1-5 attended 2-5 exercise sessions and subjects with ID 6-23 attended 6-16 sessions.

The EXERPHARMA trial (paper IV)

Primary outcome

At follow-up, no within-group or between-group changes in the primary outcome, Knee Index during gait, were observed for the two groups (-0.07 [-0.17; 0.04] Nm/(BW×HT%) (Figure 15).

Secondary outcomes

No significant between-group difference was observed for KAM (-0.09 [-0.23; 0.04] Nm/(BW×HT%). However, there was a statistically significant increase in KAM during gait after intervention for the NEMEX-group (0.12 [95%CI, 0.03; 0.22] Nm/(BW×HT%) (Figure 15). Small to moderate effect sizes (effect sizes: 0.05 – 0.53) and mostly statistically significant, but clinically non-relevant, within-group changes were seen in the majority of the KOOS subscale scores and some of the functional tests in both treatment groups with no statistically significant differences between groups (Figure 15).

Only 17 and 14 participants from the Pharma-group and NEMEX-group, respectively, were able to conduct the one-leg rise from a stool test according to the description [102]. As a consequence, no imputation on the data was performed and the statistical analyses were performed 'as observed' (Figure 15).

Explorative outcomes

No within nor between-group changes were observed for walking velocity. Small significant within-group changes (effect sizes: 0.05-0.09) were observed for the remaining explorative outcomes but no between-group differences were seen (Figure 15).

Adverse events

No between-group risk differences in adverse events were observed for the following categories; Abdominal and intestinal, Musculoskeletal symptoms, Central nervous system and psychiatric symptoms, Skin and subcutaneous symptoms, and Miscellaneous symptoms demonstrated (data not shown).

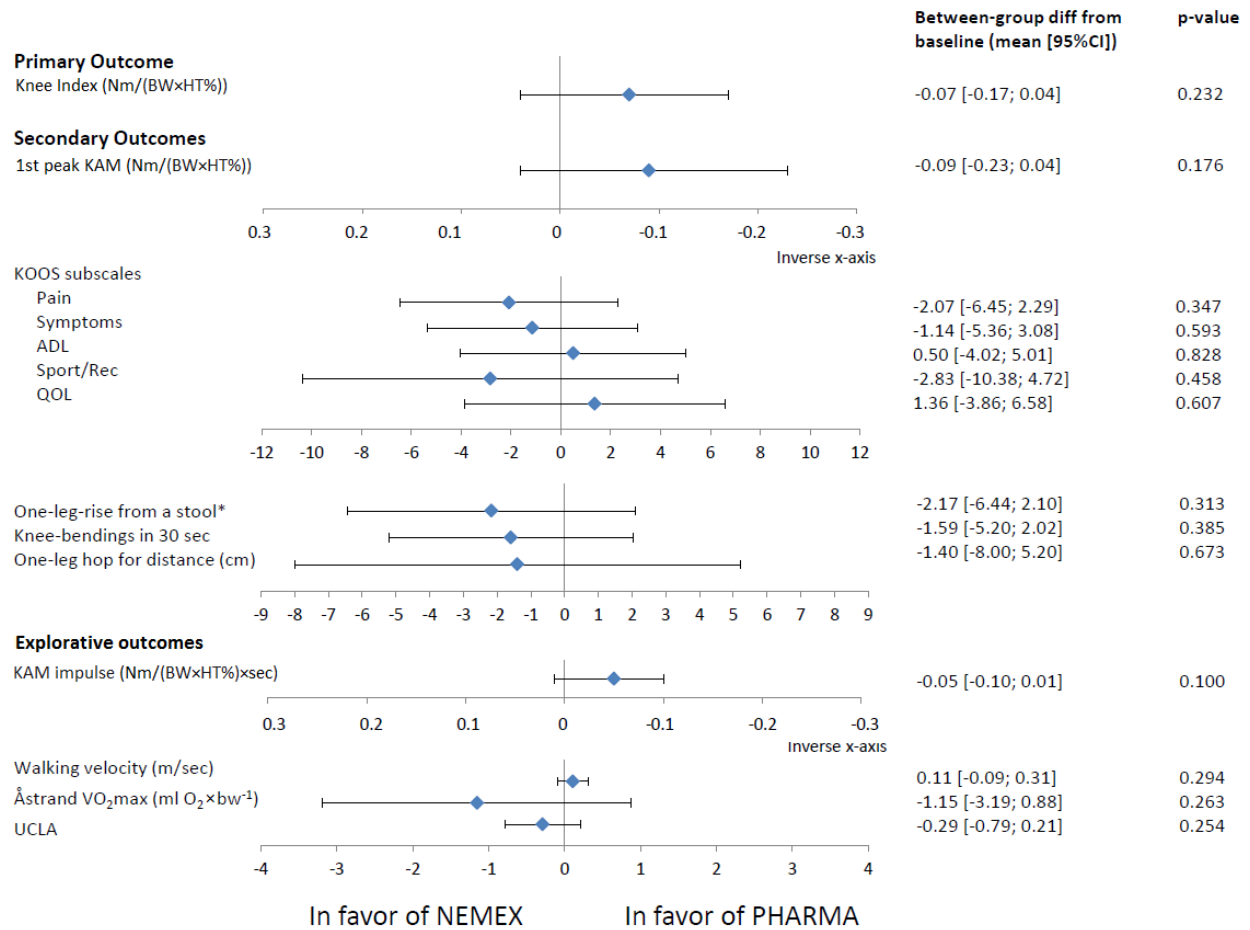


Figure 15: The between-group changes for primary and secondary outcomes. Values are presented as between-group difference from baseline and 95% confidence intervals (mean [95%CI]). Note that x-axes for Biomechanical outcomes of walking and one-leg-rise from a stool are inverted. Abbreviations are: external knee adduction moment (KAM), external knee adduction moment impulse (KAM impulse), Knee injury and Osteoarthritis Outcome Scores (KOOS) for pain, symptoms, activities of daily living (ADL), sport and recreation (Sport/rec), knee-related quality of life (QOL), Åstrand maximal endurance capacity (Åstrand VO₂max) and the University of California at Los Angeles Activity score (UCLA).

*One-leg rise from a stool was only collected n =17 for the Pharma-group and n = 14 for the NEMEX-group, and consequently, the statistics are performed 'as observed' (no imputation).

Discussion

Main findings

The main findings of this thesis were that the Knee Index (paper I), a novel index of total knee joint load, was primarily composed of moments in the frontal and sagittal planes. In addition, a large inter-subject variation in composition was observed, indicating that there are two knee-loading strategies in subjects with mild to moderate knee OA.

Secondly, the neuromuscular exercise program (NEMEX-KOA) (paper II) was found to be feasible for subjects with mild to moderate knee OA in terms of most subjects being able to progress to more complex levels of difficulty for most of the neuromuscular exercises with few incidents of short-term increase in pain from exercise.

Thirdly, the EXERPHARMA trial (papers III and IV) was designed to evaluate the possible difference in joint load-modifying effects of two common primary care interventions provided to patients with knee OA. These two interventions, NEMEX-KOA compared with information on recommended use of analgesics and anti-inflammatory drugs, which could potentially have opposite effects on the knee joint load. Due to poor adherence, especially in the Pharma-group, and a similar intake of pain relief medication in both groups, we essentially compared the addition of 8 weeks of NEMEX-KOA to 'care as usual'. We found a 2.6% non-significant and clinically irrelevant increase in the Knee Index in the NEMEX-group, no change in the Pharma-group, and no significant or clinically relevant difference between treatment groups. The results for the secondary outcomes of 1st peak KAM supported the primary finding.

Methodological considerations

Study design

This thesis employs study designs of low to high levels of evidence. Paper I used a cross-sectional design and paper II used a case series design, both of which result in a low level of evidence. Papers III and IV employ the rigorous randomized controlled trial design that results in a higher level of evidence [131].

Paper I was based on a cross-sectional design and it was reported according to the STROBE Statement [132], but due to the design, we could not infer causality. The intention was, instead, to produce associations to indicate if the novel outcome, the Knee Index, is a sensitive and responsive outcome, which can be used in OA research in the future [133].

Paper II was based on a case series design, reported according to the CARE Statement [134], but due to the design, it was not possible to state or compare the effect of the NEMEX-KOA program with other interventions or with a control group. The intention was, instead, to describe the NEMEX-KOA program in detail and to demonstrate its feasibility (with respect to progression, exertion, pain, adverse events and adherence) for subjects with mild to moderate knee OA.

Papers III and IV were based on a randomized controlled trial design and they were reported according to the CONSORT Statement [101] with a rigorous study design. Inclusion criteria were kept wide to reflect daily clinical practice. However, our study has limitations. The 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 analyses were masked to group allocation. Adherence to interventions was relatively low, which may impact the internal validity, but nevertheless, reflect daily practice and hence, a pragmatic design. Thus, in combination with wide inclusion criteria the generalizability of the current findings is considered high.

Subjects

The subjects were recruited from two settings: referral from GPs and from advertising in, for example, the local newspaper. It is likely that we recruited from two different populations, as the numbers needed to screen for subjects referred from GPs were 1.7 and 7.3 for subjects recruited from advertisements. Recruitment from two populations is likely to have increased the heterogeneity of the current sample and as a result, increased the generalizability of the results from the randomised controlled trial.

Inclusion and exclusion criteria

Inclusion criteria were kept wide to reflect daily clinical practice. Subjects with mild to moderate clinical signs of knee OA were included in this thesis, therefore the ACR [11] and EULAR [12] criteria for clinically diagnosing knee OA were combined. Structural changes on radiographs were not part of the diagnosis because generally, only about half the people with mild knee OA symptoms have structural changes on radiographs [135]. In order to test the effect of two pain-relieving treatments for knee OA, we included subjects with mild or stronger knee pain, corresponding to a cut-off of ≤ 80 on the KOOS pain subscale. In order to reduce variation in the primary outcome, the Knee Index, we chose a cut-off of a BMI of less than 32, to minimize skin movement, based on previous findings [136]. We chose to exclude subjects with recent and planned surgery to the knee and ACL reconstruction at any time point, because little is known about how these treatments influence gait kinematics and kinetics. Additionally, individuals with joint replacement of the lower limb or high tibial osteotomy were excluded, since these people have severe OA of the ankle, knee or hip.

Outcomes

Choice of biomechanical outcomes

Although, there is no consensus on which biomechanical variables to report from intervention studies, and the fact that the causation between knee joint loading and the structural progression of knee OA is limited, the current body of evidence indicates that knee joint biomechanics during walking provide important information related to mobility limitations, and that gait analyses is a sensitive tool for detection of even subtle changes [137].

To investigate potential changes in net knee moments, we chose the Knee Index as our primary outcome for the EXERPHARMA trial (papers III and IV). The Knee Index was chosen as changes in the

external moment are known to occur in the sagittal plane before, and without accompanying, changes in the frontal and/or transverse plane [51, 69, 108].

Other similar indices of knee joint forces in three planes include a recent randomized controlled trial that demonstrated a 4.5% increase in knee loading during walking in persons with knee-related limitations following a rosehip powder intervention compared with placebo by means of the total Knee Reaction Moment [137]. The interpretation of the total Knee Reaction Moment is similar to the Knee Index in the present study, albeit there are differences in the computational approach [137].

We have shown that the Knee Index is primarily composed of frontal and sagittal moments, and we identified two knee-loading strategies (sagittal or frontal plane strategy) in a sub-sample of the current study population (paper I). Why subjects with mild to moderate knee OA adopt different knee-loading strategies is difficult to elucidate from the current data. A recent study demonstrated that the frontal plane ground reaction force-to-knee lever arm accounted for 30% of the increase in KAM in patients following arthroscopic partial meniscectomy [82]. This may also be the case for the current study since both dynamic and static knee frontal plane angles (outcomes that are associated with the lever arm) in the frontal knee-loading sub-group were associated with the Knee Index and to a higher degree than for the sagittal strategy sub-group. Thus, knee alignment (static or dynamic) is most probably a key determinant of knee-loading strategy and a shift from a sagittal plane-loading strategy to a medio-lateral direction is most likely associated with knee alignment. Consequently, previous OA research that has focused on frontal or sagittal plane outcomes alone and has demonstrated no effect after interventions [79, 138] may have suffered from not capturing a possible response in a group who demonstrate a loading strategy where changes will not be captured by a single plane outcome of joint load. To improve our understanding of different knee-loading strategies, future studies should consider reporting joint loads for the sagittal and frontal planes separately, as well as in combination.

As secondary and explorative outcomes, we reported 1st peak KAM and KAM impulse during walking for the EXERPHARMA trial (papers III and IV). These were chosen to report biomechanical outcomes that are widely used in OA research. Finally, the choice of combining objective and patient-reported outcomes resulted in four domains as recommended: pain, functional performance, patient global assessment and joint imaging [139].

Functional performance

The functional performance tests were chosen for their applicability to the population and ease of use in a clinical setting. Despite this, only 35 of the 93 subjects (20 from the Pharma-group) performed the maximum number of one-leg rises from a stool test successfully one or more times at both baseline and/or follow-up. At baseline, subjects performed a median of three rises for the current study, which is much fewer than previously reported (17-25 one-leg rises) in a younger population with chronic knee pain [112].

Observed results from both the maximum number of knee-bends in 30 seconds and one-leg hop for distance tests, were in line with previous results reported for a younger meniscectomized population [113, 116] and an older population with moderate to severe knee OA [42, 140].

Progression in NEMEX-KOA

Progression in exercise difficulty was presented as the performed level of difficulty of each individual exercise at first, median and last exercise session in order to illustrate the progression through the complete intervention (8 weeks) and to indicate if an exercise held enough levels of difficulty, or suffered from floor or ceiling effects. Traditional methods such as cardiac-output for aerobic exercise and load for resistance training are not applicable for measuring and dictating progression in NEMEX, in that NEMEX aims at improving sensorimotor control and obtaining functional joint stabilization.

The exercise difficulty increased with each level (3 to 4 levels), and examples of how an increase was produced included changing to a softer more challenging surface during a weight-bearing exercise, or increasing the load or a combination of both. Although each level was associated with increased complexity, the increase in complexity might not be linear (i.e. the amount of increase from level one to level two was not necessarily similar to the amount of increase from level two to level three, etc.).

3D motion analysis

The gait laboratory upgrade during the inclusion period that was mentioned earlier does not influence our biomechanical findings. The primary reasons for variation and errors in gait laboratories are largely related to marker placement (for this laboratory, MDC 19.3%) and within-subject variation ($\approx 7\%$ was reported in paper I) and only to a small degree to hardware (error measure $< 2.0\text{mm} \approx 0.5\%$) [141].

Walking speed is known to effect gait parameters (especially sagittal plane moments) [142]. The gait trials were collected at standardized speed (close to a predetermined velocity ($\pm 5\%$)) to allow the investigation of a potential altered 'true knee-loading strategy'. Consequently, our findings should be generalized with caution, especially in comparison with trials using no methods or other methods for controlling for speed [142].

Unreported outcomes

There was a discrepancy between the ClinicalTrials.gov registration and the published study protocol (paper III) [102]. As a consequence, paper IV did not report the secondary biomechanical outcomes during one leg rise as stated in the study protocol, and the secondary outcomes (pain level measured with text messaged, UCLA and Åstrand VO_2max) were defined as 'not pre-specified outcomes'.

The EXERPHARMA trial included biomechanical outcome variables (Knee Index, 1st peak KAM and KAM Impulse) obtained during one-leg rise from a stool and patient-reported outcomes (text messages: adverse events, global perceived effect, patient-acceptable symptom state and treatment since the end of the intervention), outcomes (SF-36 and EQ-5D) collected at 8-weeks follow-up and all outcomes collected at 52-weeks follow-up, were not reported in this thesis or the papers it is based upon. These outcomes are planned to be reported in further studies based on follow-up data and secondary analyses from the EXERPHARMA trial.

Missing observation (papers IV)

Only a few missing measurements were reported in this study. A total of 8 subjects (5 from the Pharma-group) were unavailable for 3D motion analysis and intention to treat analysis, and a total of 11 subjects (3 from the Pharma-group) were unavailable for patient-reported outcomes. Thus 85 subjects (41 from the Pharma-group) were available for the primary analysis, the sample size calculation required 42 subjects in each group, and thus the current study was adequately powered.

This study had an acceptable response rate for patient-reported outcomes. The KOOS questionnaire at follow up had a response rate of 87.3% (Pharma-group 90.4% and NEMEX-group 84.3%). The response rate for drug use diary was \approx 86% (Pharma-group 85% and NEMEX-group 87%). These indicate that our study does not suffer from reporting bias.

Interventions

Progression in neuromuscular exercises (paper II)

As expected, the subjects progressed differently for the individual exercises in the NEMEX-KOA program. We observed that subjects attending six or more exercise sessions progressed to more complex levels of difficulty. Although, there are methodological differences, our findings are supported by the literature, which reports that greater exercise attendance is positively related to physical function [31, 143].

To reduce the risk of ceiling effects with long-term adherence to NEMEX-KOA, we recommend having a variety of levels for progression in exercises with a focus on functional performance. For the exercises where only a few subjects were able to progress to the highest level of difficulty, adding smaller intermediate levels may have helped subjects to progress.

Exercises that included jumping were clearly a hindrance for progression. An *in vitro* study has shown that cartilage at early stage OA is most sensitive to high loading rates (comparable to jumping activities) [144]. Consequently, exercises containing jumping should only be performed with great caution and under supervision.

Pain related to neuromuscular exercise (paper II)

A pain level of >5 VAS points after one or more exercise sessions was reported by 3 of the 23 subjects, which was in line with previous results reported for a younger population with degenerative meniscus tears [145] and an older population performing NEMEX prior to total joint replacement [41] of 5% and 32%, respectively. In terms of increased pain after an individual session, NEMEX-KOA is as safe as NEMEX for total joint replacement. For comparison, in studies of aerobic and resistance training, increase in knee pain has been reported by 8-18% of subjects with knee OA performing aerobic [146] or resistance [79, 147] training. In these studies, increase in knee pain was measured with a variety of methods ranging from logbooks to reports by instructors and reports of dropouts. Even though a direct comparison to our study is problematic due to methodological differences, NEMEX-KOA seems to be as safe as any other exercise intervention for subjects with mild to moderate knee OA.

Effect of NEMEX-KOA and Pharma on Knee Index (paper IV)

Potentially, the two interventions could affect knee joint load in opposite directions. Since the compliance was poor (only 7% had good compliance) in the Pharma-group, there was a possibility that the lack of difference between-groups was caused by poor compliance. The within-group changes can help shed light on this question. The Pharma-group, with poor compliance, showed no within-group change in knee joint load (-0.01 [-0.08; 0.07]). In the NEMEX-group, where 49% had good compliance, we found a small increase (0.06 [-0.02; 0.12]). A post hoc analysis found low correlation ($r < 0.17$) between change in outcomes of knee joint loading (Knee Index, 1st peak KAM and KAM impulse) and the number of attended exercise sessions indicating that compliance to exercise apparently did not affect alterations in knee loading to a large extent.

It should be emphasized that the within-group changes (group mean values and 95% CI) in Knee Index are within the estimated error margin (MDC = 19%) and much lower than a previously reported 13.5% increase in response to NSAID (that is, Celecoxib) treatment in comparison with placebo [69] and the a priori defined 27% change for the sample size calculation. Consequently, the present within-group changes of 0.4% and 2.6% in biomechanical loading should be considered minute and clinically irrelevant.

No between-group differences in KOOS sub-scores and functional tests were observed. The within-group effect from NEMEX was not as strong as expected based on prior literature [40, 42, 46]. However, it cannot be excluded that the NEMEX group experienced a clinically relevant difference in terms of self-reported Sport and Recreation function and some functional performance tests.

Adherence to interventions (paper IV)

Achieving and maintaining adherence to exercise interventions is important if beneficial effects of exercise are to be realized [148]. However, adherence to health interventions is a complex challenge, especially for individuals with chronic conditions [148]. The current study demonstrated an adherence to exercise that was relatively low, since only 49% fulfilled the pre-defined good compliance of ≥ 12 sessions. This is lower than the 74% and 93% adherence to exercise in patients scheduled for total joint replacement, previously shown in studies from our research group [42, 149] and may be partly explained by our subjects being younger (≈ 58 years), more fit to work ($\approx 52\%$ working full-time or part-time) and only moderately affected by OA (≈ 10 -20 points better KOOS scores) in comparison with the above-mentioned studies. In addition, our study used a pragmatic approach and exercise was performed at private clinics supervised by local physiotherapists as opposed to training performed at research institutions by project staff. This may further have affected adherence negatively.

Only three subjects (7%) in the Pharma-group demonstrated good compliance to the drug treatment intervention. Subjects received information on how best to use acetaminophen and oral NSAIDs, in doses consistent with Danish guidelines [18] but were not obliged to take certain doses. Thus, the pharmacologically-initiated pain relief was most likely not large enough to induce either increased knee moments as previously seen in subjects with knee OA [36, 87-89, 91] or dose-dependent adverse effects as observed in other trials [23-25].

Conclusions

There was a large variation in the composition of the Knee Index, it was primarily composed of the frontal and sagittal planes, indicating that some subjects with mild to moderate knee OA have a frontal, while others have a sagittal, moment-dominated strategy. The sub-group with a sagittal strategy was associated with both sagittal and frontal plane moments and angles, whereas the sub-group with a frontal strategy was associated with only frontal plane moments and angles.

An 8-week neuromuscular exercise program for individuals with mild to moderate knee OA (NEMEX-KOA) was shown to be feasible in terms of progression, exertion, pain, adverse events and adherence. Most subjects were able to progress to more complex neuromuscular exercises. Jumping activities were however generally not feasible. Those subjects attending a greater number of exercise sessions were able to progress to higher levels of difficulty and reported a larger decrease in pain. There were limited numbers of incidences of temporary increase in exercise-related pain.

The EXERPHARMA trial evaluated the possible joint load-modifying effects of a neuromuscular exercise program compared with information on the recommended use of analgesics and anti-inflammatory drugs. Due to poor adherence, especially in the Pharma-group, and a similar intake of pain relief medication in both groups, we essentially compared the addition of 8 weeks of neuromuscular exercise to 'care as usual', which did not result in reduced knee joint load during walking and no between-group differences in pain, symptoms and functional performance.

Clinical implications and future perspectives

Variation in knee OA loading strategy should be taken into consideration when evaluating OA research in middle-aged subjects with mild to moderate knee OA. Therefore, further research on index measures of total knee joint load such as the Knee Index, are needed. Additionally, further research should be conducted on how well index measures of total knee joint load are associated with compressive knee joint force and progression of knee OA.

We showed that the current neuromuscular exercise program (NEMEX-KOA) for individuals with mild to moderate knee OA was feasible and effective on improving symptoms and physical performance. Prior to broader use of NEMEX-KOA, substituting jumping activities with activities with a low impact on landing should be considered.

This effectiveness trial showed that neuromuscular exercise will have limited clinical impact on reducing knee joint load in the current setup where individuals with mild to moderate knee OA attend exercise sessions at private clinics, where compliance is likely to be low. Therefore, it is of continued interest to investigate if neuromuscular exercise is efficacious in reducing knee joint load in individuals with mild to moderate knee OA, in order to improve our understanding of load-amendable interventions.

Summary

Background

Knee osteoarthritis (OA) is a mechanically-driven disease. It is suggested that medial tibiofemoral knee-joint load increases with pharmacological pain relief, indicating that pharmacological pain relief may be positively associated with disease progression. Treatment modalities that can both relieve pain and reduce knee-joint load would be preferable. The knee-joint load is influenced by functional alignment of the trunk, pelvis, and lower-limb segments with respect to the knee, as well as the ground-reaction force generated during movement. Neuromuscular exercise (NEMEX) can influence knee joint load and decrease knee pain. It includes exercises to improve balance, muscle activation, functional alignment, and functional knee stability.

The overall aim of this thesis was to compare the effectiveness of a specific neuromuscular exercise program with optimized analgesics and anti-inflammatory drug use on knee joint loads, as well as pain and functional performance in individuals with mild to moderate medial tibiofemoral knee OA.

A biomechanical outcome of total knee joint load has not yet been described in detail. Therefore the first study (paper I) of this thesis assessed the Knee Index, a novel measure of total knee joint load that incorporates all three planes, and has been shown to be sensitive to changes in pain in subjects with moderate knee OA. However, the relative contribution and inter-subject variation of each plane to the Knee Index has not previously been described. Additionally, associations between the Knee Index and other biomechanical variables have not been described to indicate if the Knee Index is a sensitive and responsive biomechanical outcome suitable as a primary outcome in a randomized controlled trial.

A NEMEX program specifically designed for subjects with mild to moderate knee OA has not previously been described. Therefore, in a randomized controlled trial, the second study (paper II) described the feasibility of the current NEMEX for subjects with mild to moderate knee OA (NEMEX-KOA), in terms of progression, pain, exertion, adverse events and adherence, to indicate if NEMEX-KOA could be a suitable intervention for subjects with mild to moderate knee OA.

The third study (papers III and IV) described and reported a pragmatic randomized controlled trial (the EXERPHARMA trial), that was designed to investigate the effectiveness of NEMEX-KOA, compared with optimized analgesics and anti-inflammatory drug use (Pharma), on the measures of knee-joint load (Knee Index) in individuals with mild to moderate medial tibiofemoral knee OA.

Method

We performed a randomized, single-blind, clinical trial comparing NEMEX-KOA with Pharma (papers I, II, III and IV). Subjects with mild to moderate medial knee OA were recruited from general medical practices in the community of Odense and Middelfart, Denmark, and from advertisements in local clubs, libraries, print media, and Facebook, and were randomly allocated (1:1) to one of two 8-week treatments, either to (a) exercise therapy twice a week (the NEMEX-group), or to (b) a pamphlet and video materials with information on the recommended use of analgesics and anti-inflammatory drugs (acetaminophen and oral NSAIDs) (the Pharma-group). The primary outcome was change in the Knee Index during walking after 8 weeks of intervention. Secondary and exploratory outcomes included changes in Knee Injury and Osteoarthritis Outcome Score (KOOS), UCLA Activity score and functional

performance tests (maximum one-leg rises from a stool, maximum number of knee-bends in 30 seconds and one-leg hop for distance).

For the cross-sectional study (paper I), we calculated the Knee Index using 3-dimensional gait analysis in a sample of the first 44 subjects, aged 40-70 years with mild to moderate knee OA, recruited for the randomized controlled trial. Subjects were instructed to walk at a self-selected speed and the average of the 1st peak Knee Index for five successful gait trials was subsequently used in the analysis.

The case series study (paper II) reported on the first 23 subjects randomized to the 8-week twice weekly NEMEX-KOA regime, including 11 exercises with 3-4 levels of difficulty. The level of difficulty was noted for each exercise in every session. Exertion, pain, adverse events and adherence were recorded at each session.

Results

In total, 93 subjects (57% women, 58 ± 8 years with a BMI of 27 ± 4) were randomized to the Pharma-group ($n = 46$) or the NEMEX-group ($n = 47$) with data from 41 and 44 patients, respectively, available at follow up.

The Knee Index was mainly composed of frontal and sagittal plane moments, with a large inter-subject variation in the composition. This resulted in additional post-hoc association analyses dividing the sample into sub-groups (frontal or sagittal plane dominance). The sub-group analyses resulted in better associations than the analyses conducted on all individuals.

The 18 subjects that participated in six or more sessions progressed at least one level of difficulty in half or more of the exercises. However, few subjects were able to progress to jumping activities. Exertion ranged from 'light' to 'very heavy'. Four subjects reported a clinically relevant increase in short-term pain. No musculoskeletal adverse events were reported. Notably, three of 23 subjects dropped out giving knee pain as the reason. Their pain ratings were, however, not getting worse.

The Knee Index during gait showed a statistically significant increase immediately after the 8-week intervention for the NEMEX-group, corresponding to a statistically non-significant between-group difference. Despite within-group improvements in most KOOS subscale scores and functional performance in both treatment groups, no statistically significant between-group differences were observed.

Conclusion

From this thesis, I conclude that despite large variation in the composition of the Knee Index, it was primarily composed of the frontal and sagittal planes. The Knee Index therefore holds promise as both a sensitive and responsive biomechanical outcome for the evaluation of total knee joint load.

Furthermore, the NEMEX-KOA program was found feasible for subjects with baseline mild to severe knee pain. Subjects were able to progress in level of difficulty with few reports of clinically relevant increase in pain and no adverse events. Jumping activities were however not feasible. These findings hold promise for investigating the effectiveness of NEMEX-KOA in individuals with mild to moderate OA. Due to poor adherence, especially in the Pharma-group, and a similar intake of pain relief medication in both groups, the EXERPHARMA trial essentially compared the addition of 8 weeks of neuromuscular exercise to 'care as usual', which did not result in reduced knee joint load during walking and no between-group differences in pain, symptoms and functional performance.

Resumé [Danish]

Baggrund

Knæartrose er en mekanisk drevet sygdom. Det formodes, at belastningen over det mediale tibiofemorale ledkammer stiger med anvendelsen af farmakologisk smertelindring, hvilket indikerer, at farmakologisk smertelindring kan være positivt associeret med sygdomsprogression. Behandlingsmetoder der kan smertelindre og reducere belastningen over knæleddet vil være at foretrække. Belastningen over knæleddet påvirkes af den funktionelle alignment af torso, bækken og benets segmenter, i forhold til knæet, samt reaktionskraften fra underlaget dannet under bevægelse. Neuromuskulær træning (NEMEX) kan påvirke belastningen over knæleddet og mindske smerter i knæet. Træningen omfatter øvelser til at forbedre balance, muskel aktivering, funktionel alignment og funktionel knæstabilitet.

Det overordnede formål med denne afhandling var at sammenligne effekten, af et specifikt neuromuskulært træningsprogram med optimeret anvendelse af analgetika og anti-inflammatoriske lægemidler, på den samlede belastning over knæleddet, samt smerter og fysisk funktion hos personer med mild til moderat knæartrose.

Et biomekanisk effektmål til at måle den samlede belastning over knæleddet, er endnu ikke blevet beskrevet i detaljer. Derfor omhandlede det første studie (artikel I) i denne afhandling, vurderingen af Knee Index, et nyt effektmål af den totale belastning over knæleddet, som består af alle tre planer. Knee Index har vist sig at være sensitiv nok, til at kunne detektere ændring i knæsmerter hos personer med moderat knæartrose. Det er imidlertid uvist, i hvilket omfang hvert plan bidrager til Knee Index og hvor stor variation der er mellem deltagere. Associationer mellem Knee Index og andre biomekaniske variable har aldrig tidligere været beskrevet. Med denne viden kan vi få en indikator for, om Knee Index kan være et sensitivt og svarfølsomt biomekanisk effektmål, som ville kunne anvendes som primært effektmål i et randomiseret kontrolleret forsøg.

Et NEMEXs program designet til personer med mild til moderat knæartrose er ikke tidligere blevet beskrevet. Hvorfor den anden undersøgelse (artikel II) i denne afhandling, indeholdt en beskrivelse af anvendeligheden af nærværende NEMEX program til deltagere med mild til moderat knæartrose (NEMEX-KOA). Anvendeligheden blev vurderet ud fra progression, smerte, anstrengelse, utilsigtede hændelser og fastholdelse til programmet (compliance). Således kan det vurderes, om NEMEX-KOA ville kunne være en passende intervention til personer med mild til moderat knæartrose i et randomiseret kontrolleret forsøg.

Den tredje undersøgelse (artikler III og IV) beskrev og rapporterede et pragmatisk randomiseret kontrolleret forsøg (EXERPHARMA studiet), som blev designet til at undersøge effekten af NEMEX-KOA, sammenlignet med optimeret anvendelse af analgetika og anti-inflammatoriske lægemidler (Pharma), på den samlede belastning over knæleddet (Knee Index) hos personer med mild til moderat tibiofemoral knæartrose.

Metode

Vi udførte et randomiseret, enkelt-blindet, klinisk studie, der sammenlignede NEMEX-KOA med Pharma (artikler I, II, III og IV). Deltagere med mild til moderat knæartrose blev rekrutteret fra almen praksis, i Odense og Middelfart kommune i Danmark, og via annoncer i lokale foreninger, biblioteker, trykte medier og Facebook. Deltagerne blev tilfældigt fordelt (1:1) til en af to 8-ugers behandlinger, enten (a)

NEMEX-gruppen; to træninger ugentligt eller (b) Pharma-gruppen; information om den anbefalede brug af analgetika og anti-inflammatoriske lægemidler (paracetamol og tablet NSAID) via folder og videomateriale. Det primære effektmål var ændring i Knee Index under gang efter 8 ugers intervention. Sekundære og eksplorative effektmål var bl.a. ændringer i symptomer målt via Knee Injury and Osteoarthritis Outcome Scores (KOOS), UCLA Aktivitets score og tests af funktionel præstation (maksimalt antal et-bens oprejsninger fra taburat, maksimalt antal knæbøjninger på 30 sekunder og et-bens hop for afstand).

I tværnsnitsundersøgelsen (artikel I) beregnede vi Knee Index via 3-dimensionel ganganalyse, i en stikprøve af de første 44 personer rekrutteret til det randomiserede kontrollerede forsøg, i alderen 40-70 år med mild til moderat knæartrose. Deltagerne blev instrueret i at gå med selvvalgt hastighed. Knee Index blev analyseret som gennemsnittet af den første spidsbelastning efter hæl-isæt, for 5 vellykkede gang forsøg.

I case-serie studiet (artikel II) beskrev vi de første 23 deltagere, som blev randomiseret til 8-ugers NEMEX-KOA med to ugentlige træningssessioner, indeholdende 11 øvelser i 3-4 sværhedsgrader. Sværhedsgraden af hver enkelt øvelse ved hver session blev registreret. Anstrengelse, smerte, utilsigtede hændelser og compliance blev ligeledes registreret ved hver træningssession.

Resultater

I alt blev 93 deltagere (57% kvinder, 58 ± 8 år med et BMI på 27 ± 4) randomiseret til enten Pharma-gruppen ($n = 46$) eller NEMEX-gruppen ($n = 47$); data fra henholdsvis 41 og 44 deltagere var tilgængelige ved opfølgning.

Knee Index var hovedsageligt sammensat af momenterne fra det frontale og sagittale plan, med store inter-individuelle variationer i sammensætningen. Dette resulterede i yderligere post hoc associationsanalyser, hvor vi inddelte stikprøven i to undergrupper (domineret af henholdsvis det frontale eller sagittale plan). Analysen af undergrupperne, resulterede i bedre associationer end for analyser baseret på hele gruppen.

De 18 deltagere, der deltog i 6 eller flere træningssessioner, progredierede mindst én sværhedsgrad i halvdelen eller flere af øvelserne. Hvorimod, kun få deltagere var i stand til at progrediere til aktiviteter indeholdende hop. Anstrengelsesniveauet for træningsprogrammet varierede fra "let" til "meget tungt". Fire deltagere rapporterede en klinisk relevant forværring af kortvarige knæsmerter. Ingen muskuloskeletale utilsigtede hændelser blev rapporteret. Bemærkelsesværdigt er det, at 3 af 23 deltagere faldt fra i løbet af interventionen, de begrundede frafaldet med knæsmerter. Deres smerte rapportering viste imidlertid ingen forværring.

Knee Index under gang steg statistisk signifikant lige efter 8 ugers intervention for NEMEX-gruppen svarende til en statistisk ikke-signifikant forskel mellem grupperne. Begge grupper rapporterede forbedringer på de fleste KOOS subskalaer og funktionelle præstationer. På trods af dette, fandtes ingen statistisk signifikante forskelle mellem grupperne.

Konklusion

Ud fra denne afhandling kan jeg konkludere, at på trods af stor variation i sammensætningen af Knee Index, bestod det primært af det frontale og sagittale plan. Knee Index er et lovende, sensitivt og svarfølsomt, biomekanisk effektmål, til vurderingen af den samlede belastning over knæledet.

Derudover, blev NEMEX-KOA programmet fundet anvendeligt, til personer med milde til svære smerter i knæet ved baseline. Deltagerne kunne progredierte i øvelses sværhedsgrad, med få hændelser af klinisk relevant forværring af knæ smerter og uden utilsigtede hændelser. Aktiviteter som indeholdt hop, var imidlertid ikke anvendelige. Disse fund indikerer, at det vil være relevant at undersøge effekten af NEMEX-KOA som intervention til personer med mild til moderat knæartrose.

På grund af lav overholdelse af interventionsregimerne, især i Pharma-gruppen, og et sammenligneligt lægemiddelforbrug i begge interventionsgrupper, endte EXERPHARMA studiet med reelt at undersøge effekten af 8 ugers neuromuskulær træning i tillæg til vanlig behandling. Undersøgelsen resulterede i, at der ikke fandtes reduktion i belastningen over knæleddet under gang. Der blev heller ikke fundet forskelle mellem grupperne for smerter, symptomer og funktionel præstation.

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