Neuromuscular Function in Meniscectomized Patients at High Risk of Knee Osteoarthritis

Research Unit for Musculoskeletal Function and Physiotherapy
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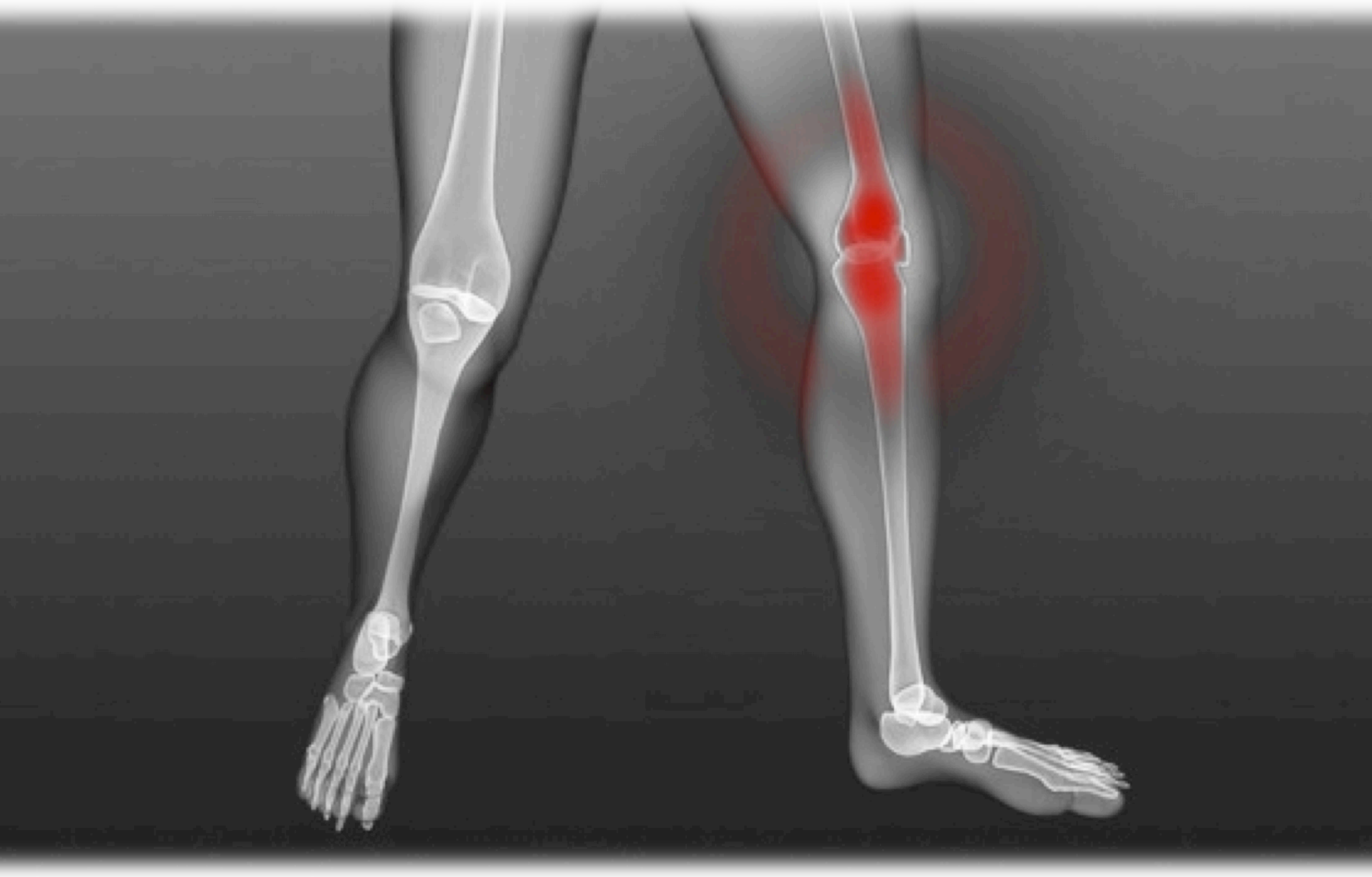

SYDDANSK UNIVERSITET
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Ph.D. Thesis

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Contents

Preface

This thesis was accomplished at the Institute of Sports Science and Clinical Biomechanics, Faculty of Health, University of Southern Denmark, Odense. Supervision was provided by main supervisor professor, PhD, Ewa M. Roos and co-supervisor professor, PhD, Per Aagaard from the Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark.

All experiments were conducted at the Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark and recruitment of patients was accomplished through the Department of Orthopedics and Traumatology, Odense University Hospital, with the help of Professor, PhD, Søren Overgaard.

The studies of which this thesis comprises was supported by The Danish Rheumatism Association and the Region of Southern Denmark.

List of papers

This thesis is based on the following three papers which will be referred to by their roman numerals in the text:

I. Thorlund JB, Aagaard P, Roos EM. Thigh Muscle Strength, Functional Capacity, and Self-Reported Function in Patients at High Risk of Knee Osteoarthritis Compared With Controls. *Arthritis Care & Research* 2010; 62(9): 1244-51

II. Thorlund JB, Roos EM, Aagaard P. Neuromuscular function during stair descent in meniscectomized patients and controls. *Medicine and Science in Sports and Exercise* 2011; 43(7): 1272-9

III. Thorlund JB, Aagaard P, Roos EM. Muscle strength and functional performance in patients at high risk of knee osteoarthritis: Changes from 2 to 4 years post meniscectomy. Revised version accepted for publication in *Knee Surgery, Sports Traumatology, Arthroscopy*, October 10, 2011.

Thesis at a glance

Paper	Question	Participants	Time since meniscectomy	Methods	Conclusion
I	Do meniscectomized patients self-report more pain and impaired function together with reduced muscle strength and reduced functional performance compared to population-based controls?	31 patients and 31 controls	2 years	Isokinetic dynamometry Functional tests KOOS questionnaire	Despite patients self-reporting more pain and reduced function compared to population-based controls no differences were observed in muscle strength and functional performance.
II	Do meniscectomized patients show altered patterns of neuromuscular activity, reduced ROM, reduced movement speed and reduced GRF during stair descent compared to controls?	22 patients and 26 controls	2 years	Force plate analysis Electro goniometry EMG	Reductions in knee ROM, movement speed and altered GRF kinetics and neuromuscular activity between patients and controls could not be confirmed. A shorter stance phase along with reduced medial vs. lateral thigh muscle activity was observed in the operated compared with the contra-lateral leg of patients.
III	Do changes in maximal muscle strength, rapid force capacity and functional performance differ between patients and controls over a 2 year period?	22 patients and 25 controls	4 years	Isokinetic dynamometry Functional tests	Longitudinal changes in knee flexor MVC, rapid force capacity and functional performance from 2 to 4 years post meniscectomy were similar in patients and controls. However, post-hoc analysis revealed differential changes in knee extensor MVC in favor of the contra-lateral leg compared with the operated leg of patients.

KOOS = Knee Injury and Osteoarthritis Outcome Score, ROM = Range Of Motion, GRF = Ground Reaction Force, EMG = Electromyography, MVC = Maximal Voluntary Contraction, RFD = Rate of Force Development

Description of contributions

PAPER I

Study design:	Jonas B. Thorlund Ewa M. Roos
Data collection:	Jonas B. Thorlund Jacob Damgaard Søren Skovbakke
Data analysis:	Jonas B. Thorlund Per Aagaard
Manuscript writing:	Jonas B. Thorlund
Manuscript revision:	Ewa M. Roos Per Aagaard

PAPER II

Study design:	Jonas B. Thorlund Ewa M. Roos Per Aagaard
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Data analysis:	Jonas B. Thorlund Per Aagaard
Manuscript writing:	Jonas B. Thorlund
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Data analysis:	Jonas B. Thorlund Per Aagaard
Manuscript writing:	Jonas B. Thorlund
Manuscript revision:	Ewa M. Roos Per Aagaard

Abbreviations

ACR	American College of Rheumatology
Act_{load}	Mean neuromuscular activity during the loading slope phase
$Act_{peakGRF}$	Mean neuromuscular activity at GRF_{peak}
ADL	Activities of Daily Living
BPM	Beats Per Minute
BF	m. Biceps Femoris
$Co\text{-}act_{load}$	Level of muscle co-activation during the loading slope phase
$Co\text{-}act_{peakGRF}$	Level of muscle co-activation at GRF_{peak}
EMG	Electromyography
GRF	Ground Reaction Force
GRF_{peak}	Peak Ground Reaction Force
KAM	Knee Adduction Moment
KOOS	Knee injury and Osteoarthritis Outcome score
$Load_{slope}$	GRF Loading Slope
MRI	Magnetic Resonance Imaging
MVC	Maximal Voluntary Contraction
OA	Osteoarthritis
QOL	Quality Of Life
RFD	Rate of Force Development
ROM	Range of motion
S_{freq}	Stride Frequency
Sport/Rec	Sport and Recreational function
ST	m. Semitendinosus
$T_{peakGRF}$	Time from foot-strike to GRF_{peak}
T_{stance}	Time for entire stance phase
VL	m. Vastus Lateralis
VM	m. Vastus Medialis
V_{mean}	Average knee joint angular velocity from foot-strike to GRF_{peak}

Introduction

Knee Osteoarthritis

Musculoskeletal diseases are the most common chronic disorders and a huge burden to society affecting more than half of the adult Danish population within any given two-week period (Statens Institut for Folkesundhed, 2007, Altman, 2010). Osteoarthritis (OA) is one of these musculoskeletal diseases. It is a slowly developing degenerative disease causing local destruction of the involved joint and the surrounding structures. The knee is the most frequently affected joint by OA (Martin, 1994) resulting in pain, functional disability and reduced quality of life (Buckwalter et al., 2004, Felson, 2009). A review from the UK estimated that about 25% of adults above 55 years self-report knee pain with half of them displaying radiographic changes of OA (Peat et al., 2001).

The structural changes observed in patients with tibiofemoral knee OA are characterized by a degradation of the cartilage on the tibial and femoral articular surfaces together with degenerative changes such as joint space narrowing, osteophytes, sclerosis and bone marrow lesions (Hunter et al., 2009, Ding et al., 2010). These changes are believed to origin from changes to the mechanical environment causing altered knee joint load (Andriacchi and Mundermann, 2006) and can be detected by radiography or Magnetic Resonance Imaging (MRI). Traditionally, knee OA has been diagnosed by radiography using different classification systems such as the Kellgren & Lawrence scale (KELLGREN and LAWRENCE, 1957) which is one of the most commonly used. Radiography is still considered the diagnostic 'gold standard'. However, the most frequent symptoms experienced by the patients such as knee pain, stiffness and functional decline are poorly associated with structural changes (Dieppe et al., 1997, Dieppe, 2004). In fact, it may take decades for structural changes to appear on radiographs even though symptoms are evident. Therefore, much research is presently conducted in using MRI as an alternative and more sensitive measure than radiography to detect OA onset (Hunter et al., 2009). Relying only on radiographs and not including patient reported pain and symptoms in the diagnosis of knee OA is problematic. The American College of Rheumatology (ACR) has developed a set of criteria for clinical diagnosis of knee OA. These criteria include age >38, knee pain, morning stiffness and joint crepitus (Altman et al., 1986). As a consequence of this, knee OA is frequently referred to as either radiographic or symptomatic knee OA depending on the criteria of diagnosis.

Several risk factors have been identified for the development of knee OA (Blagojevic et al., 2010). Some of the most studied and well defined are; age (Dillon et al., 2006), obesity (Lohmander et al., 2009), female gender (Srikanth et al., 2005), heredity (Neame et al., 2004) and previous knee injury (Gelber et al., 2000, Wilder et al., 2002, Lohmander et al., 2007). Furthermore, impaired neuromuscular function is also considered a risk factor for knee OA (Bennell et al., 2008).

The role of neuromuscular function in knee OA development

Knee OA is considered a mechanically driven disease due to increased and/or altered load. Particularly increased knee adduction moment (KAM), which is indicative of medial compartment knee joint loading (Schipplein and Andriacchi, 1991), have been associated with incidence (Baliunas et al., 2002), severity (Sharma et al., 1998) and progression (Miyazaki et al., 2002) of medial tibiofemoral knee OA. Impaired muscle strength reduces the capacity for shock absorption and joint protection. Several studies have demonstrated that patients with knee OA have reduced lower extremity muscle strength compared to healthy controls (Jan et al., 1990, Messier et al., 1992, Slemenda et al., 1997, Liikavainio et al., 2008). Particularly maximal quadriceps strength seems to be compromised (Bennell et al., 2008). Furthermore, studies have reported reduced risk of knee OA in women with moderate and high quadriceps strength (Hootman et al., 2004), a protective effect of high quadriceps strength on incident symptomatic knee OA (Segal et al., 2009) and that reduced functional capacity predict knee OA development in patients with knee pain (Thorstensson et al., 2004). Training induced changes in quadriceps strength have been shown to reduce the rate of loading in women indicating a possible role for muscle strength and training in knee OA prevention (Mikesky et al., 2000).

Alterations in neuromuscular activity are another aspect of neuromuscular function which is thought to affect knee joint kinematics and kinetics during walking gait and stair ascent/descent. Observed kinematic alterations in knee OA patients include decreased range of motion (ROM) and reduced movement speed during walking gait (Chen et al., 2003, Astephen and Deluzio, 2005) thought to reflect a movement strategy to protect the knee joint and minimize pain. Changes in neuromuscular activity in knee OA patients involve increased muscle co-activation (Childs et al., 2004, Lewek et al., 2004, Hortobagyi et al., 2005, Hubley-Kozey et al., 2008, Schmitt and Rudolph, 2008) and altered medial vs. lateral muscle activity (Hubley-Kozey et al., 2006, Heiden et al., 2009, Hubley-Kozey et al., 2009). As with impaired muscle strength changes in prime mover thigh neuromuscular activity/control could potentially affect the focal concentration of bone-on-bone contact forces in the knee joint during locomotion.

The causes of degenerative changes to the knee joint are complex and likely involve different pathways incorporating various combinations of risk factors for different sub groups of patients (Radin, 2004). Impaired neuromuscular function is considered one of the modifiable risk factors for knee OA but the exact role still remains to be determined. Figure 1 presents a possible framework containing modifiable and non-modifiable risk factors that can affect knee OA initiation through pathways mediated by neuromuscular function. Aging is associated with loss in muscle strength (Aagaard et al., 2010) together with proprioception and balance (Loeser and Shakoor, 2003) and men and women have different strategies of neuromuscular activation (Henry and Kaeding, 2001). Knee injury can affect neuromuscular function through mechanical instability, pain and disuse atrophy. Furthermore, few patients are ever fully rehabilitated after knee injury. Deconditioning of the neuromuscular system may also stem from a sedentary lifestyle which can lead to obesity that can affect loading of the knee joint directly due to increased mass (Messier et al., 2005) or indirectly through decreased neuromuscular function.

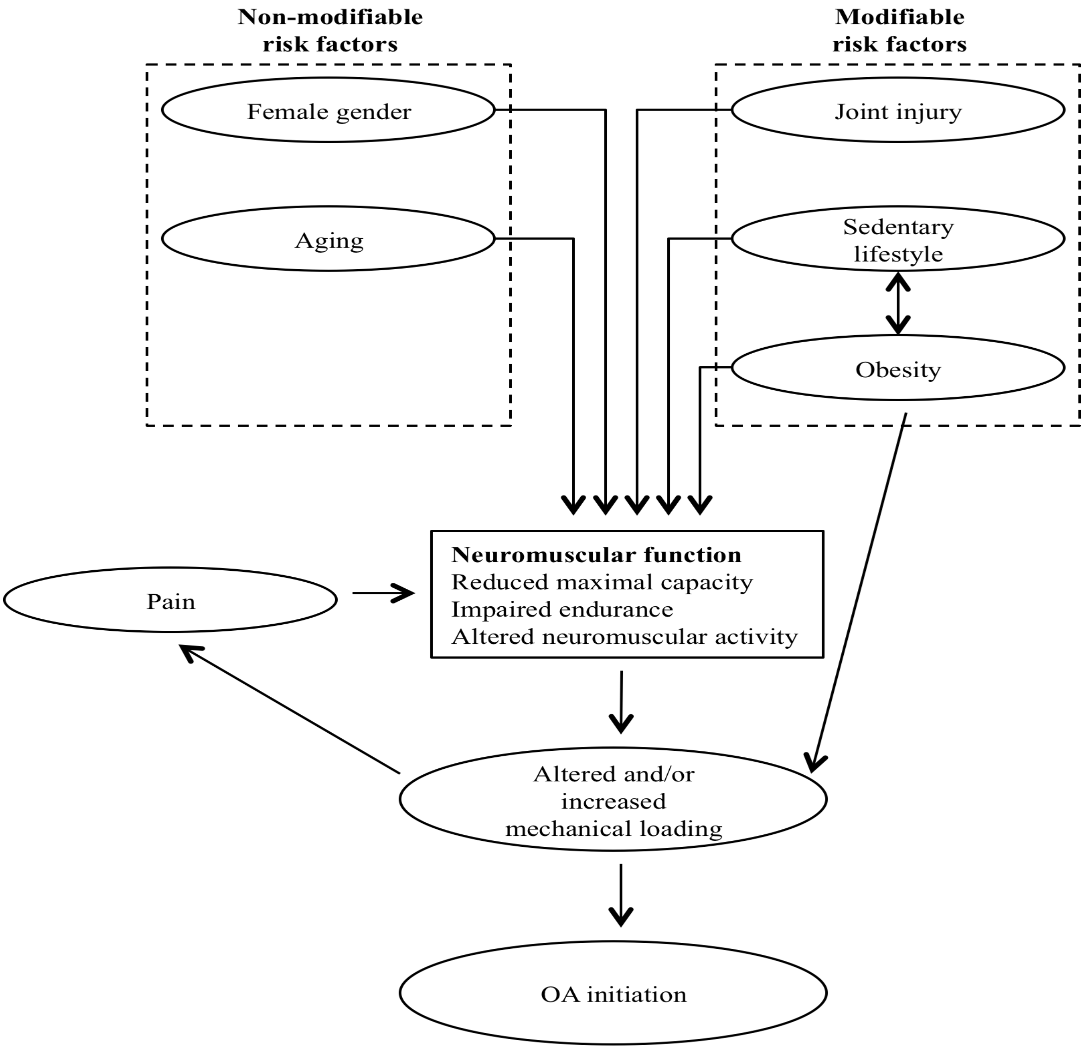

Figure 1: Risk factors of osteoarthritis which may contribute to the development of osteoarthritis through impaired neuromuscular function, inspired by Roos et al. (Roos, 2005) and Andriacchi and Mündermann et al. (Andriacchi and Mundermann, 2006).

Age is an important feature of knee OA and given future demographics with an increasing number of older people the prevalence of knee OA is expected to increase (Helweg-Larsen et al., 2009, Felson, 2009). The majority of patients have mild to moderate OA (Lohmander and Roos, 2007). Exercise, together with information and weight reduction if needed is the first line treatment (Zhang et al., 2010) and evidence-based medicine to reduce pain and improve function in these patients (Fransen and McConnell, 2008, Fransen and McConnell, 2009).

There is currently no cure for knee OA and when all other treatments fail knee joint replacement is the only alternative for end stage knee OA (Lohmander and Roos, 2007) but this procedure is expensive, has a limited lifespan and is invasive for the patient. Thus, prevention is of utmost importance to decrease the prevalence of the disease. Investigating potential deficits in lower limb neuromuscular function in patients at high risk of knee OA could expand our knowledge about the role of neuromuscular function in the initiation of knee OA. Such knowledge would be important for the future tailoring of prevention regimes to prevent or postpone knee OA development.

Meniscectomized patients as a 'pre-osteoarthritis' model

From a transverse perspective the menisci are two wedge shaped structures situated between the medial and lateral articular surfaces of the femur and tibia. They are semi-lunar shaped and constructed of fibro cartilage with exception of the ends which consists of collagen fibers attaching to the tibia through the anterior and posterior horns. The peripheral part of the meniscus is infiltrated by capillaries and unlike articular cartilage the meniscal matrix primarily comprise of Type I collagen which is arranged in a circumferential pattern (Fithian et al., 1990). The medial meniscus covers about 50% of the medial tibial plateau and is also attached to the medial collateral ligament. The lateral meniscus covers about 70% of the lateral tibial plateau and is not attached to the lateral collateral ligament making it more mobile (Rath and Richmond, 2000).

The primary functions of the menisci are to provide shock absorption and load transmission (i.e. distributing contact force over a large area of articular cartilage) during movement and joint loading (Walker and Erkman, 1975, Kurosawa et al., 1980) but the menisci may also be important for knee joint stability, proprioception and lubrication (Fithian et al., 1990). Thus, damage to the menisci compromises normal knee joint function.

The medial meniscus is more prone to injuries than the lateral meniscus (Rath and Richmond, 2000). This is thought to be due to the lower mobility of the medial meniscus caused by the long distance between its attachments (compared with the lateral meniscus) and due to its attachment to the medial collateral ligament (Fithian et al., 1990). Meniscus tears are often categorized as either traumatic or degenerative tears (Poehling et al., 1990).

Traumatic tears are typically observed in an otherwise 'healthy' meniscus of younger active individuals in relation to a sports related trauma and can be associated with anterior cruciate or collateral ligament injuries (Poehling et al., 1990). The injury often occur due to internal femur rotation as the knee moves from a flexed to a more extended position causing the meniscus to split vertically and parallel to the circumferential collagen fibers (Englund and Lohmander, 2006). This type of tear is referred to as a horizontal or bucket handle tear.

Degenerative tears are observed in middle-aged and older population and are described as horizontal cleavages, flap tears or complex tears (Poehling et al., 1990). These tears are primarily observed in the medial meniscus (Noble and Hamblen, 1975) and are common – also in asymptomatic individuals (Bhattacharyya et al., 2003, Englund et al., 2008), however the etiology is unclear. Patients undergoing surgery for degenerative tears have worse long-term outcome after meniscectomy than patients with traumatic tears (Englund et al., 2003).

Meniscus tears are one of the most common types of knee injury and meniscus surgery is the most common and an increasingly used orthopedic procedure with more than 16.000 meniscectomies performed in Denmark in 2009 (Figure 2). Studies have shown that meniscus injury in addition to other knee

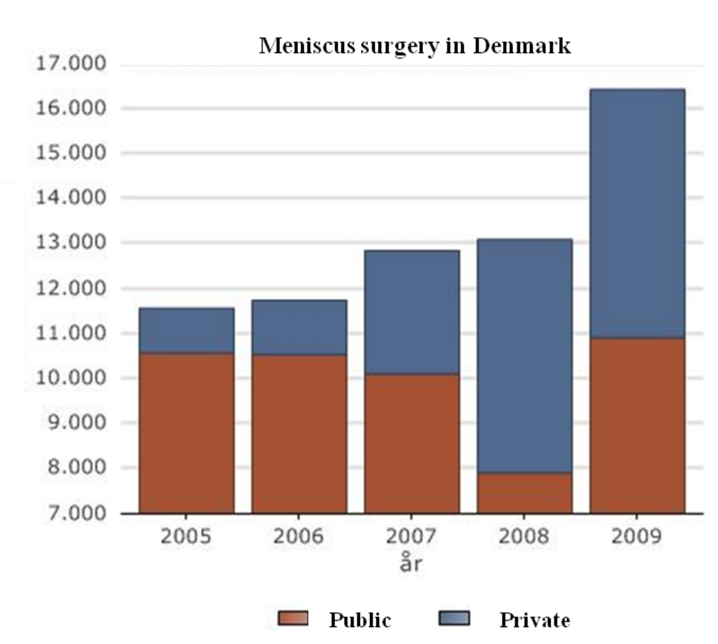

Figure 2: Number of meniscus surgeries in Denmark from 2005-2009 based on numbers from the Danish patient register ('Landspatientregisteret'), adapted from www.Altinget.dk 08-09-2010.

injuries are associated with a higher risk of knee OA compared to knee injuries without concomitant meniscus tears (Oiestad et al., 2009). Furthermore, every second meniscectomized patient show radiographic features of knee OA 10-15 years after surgery (Englund et al., 2003).

It has been suggested that degenerative tears may be associated with incipient OA or represent the initial stage of the disease in the middle-aged population (Englund and Lohmander, 2006, Englund, 2008). As such, individuals with symptomatic degenerative medial meniscus tears are a subgroup at particular high risk of knee OA and thus constitute a good model to study individuals in a 'pre-osteoarthritis' stage.

Neuromuscular function in meniscectomized patients

Varying results have been reported on muscle strength recovery after surgery in meniscectomized patients. Most studies have focused on short-term (0-6 month) recovery after surgery (Figure 3) (Durand et al., 1991, Stam et al., 1992, Matthews and St-Pierre, 1996, Gapeyeva et al., 2000, Sturnieks et al., 2008a, Glatthorn et al., 2010) and it seems that strength deficits still persist ~6 month after surgery (Gapeyeva et al., 2000, Glatthorn et al., 2010). However, most studies include a mixed population of patients with substantial variation in age, different types of meniscus tears (i.e. traumatic or degenerative) or do not specify the type of tear. Furthermore, the method of muscle strength assessment (i.e. isometric or concentric) and velocity used during isokinetic testing also vary between studies, which make comparison difficult. Deficits in short-term muscle strength may partly be caused by the surgery induced trauma as indicated by the studies by Durand et al. and Matthews & St-Pierre in Figure 3 (Durand et al., 1991, Matthews and St-Pierre, 1996). Thus, it is difficult to elucidate if strength deficits are attributed to the surgery induced trauma *per*

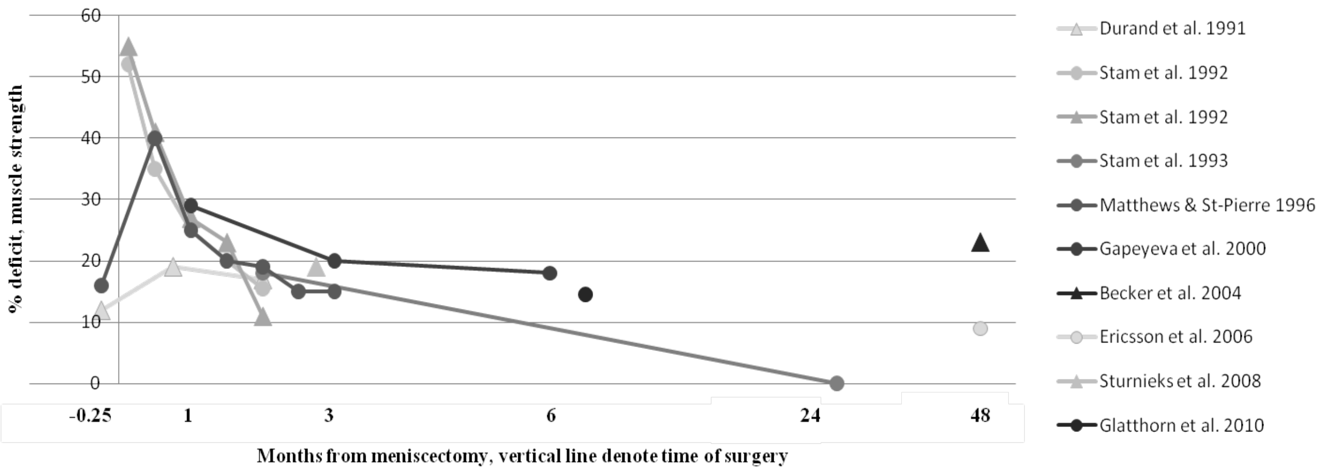

Figure 3: Overview of studies on muscle strength deficits in meniscectomized patients. Age of patients, type of meniscal tear and method of muscle strength assessment vary between studies. Triangle denote comparison of meniscectomized leg to a control group, circle denote comparison to the contra-lateral leg. Studies with connecting lines indicate longitudinal data.

se or represent potential initial stages of knee OA development in studies on the short-term recovery in meniscectomized patients. To investigate the role of muscle strength deficits in knee OA development attention should be given to studies with a longer follow-up from surgery since these patients may be considered fully rehabilitated from surgery.

A single long term (>6 month) longitudinal study has been conducted, which observed no difference in maximal knee extensor muscle strength compared to the contra-lateral leg 28 month post meniscectomy (Stam et al., 1993) (Figure 3). However, patients were military personnel and a mix of patients who had undergone partial or total meniscectomy making the results difficult to generalize. Only two long-term cross-sectional studies (~48 month post meniscectomy) have been conducted including homogeneous groups of middle-aged patients meniscectomized for symptomatic degenerative tears (Becker et al., 2004, Ericsson et al., 2006) (Figure 3). One study reported a 6-9% difference in muscle strength between the operated and the contra-lateral leg (Ericsson et al., 2006). The other study observed a bilateral deficit of >20% in maximal muscle strength between patients and controls, but no difference was observed between the operated leg and contra-lateral leg (Becker et al., 2004). The finding of a bilateral strength deficit emphasizes the need for a control group if the magnitude and nature of lower extremity muscle strength deficiencies are to be identified and examined.

Testing of maximal isometric or concentric muscle strength are often the methods of choice to assess maximal muscle strength. However, these methods may not adequately describe all aspects of lower extremity muscle function and functional performance. For instance, reduced levels of eccentric thigh muscle strength may reduce the ability to absorb impacts and thereby increase knee joint loading (Bennell et al., 2008). Furthermore, reduced capacity for rapid force production (i.e. a right shift in the torque-time curve, indicating a reduced rate of force development [RFD]) is thought to be important for functional performance (Suetta et al., 2004, Aagaard et al., 2010). Impaired rapid force capacity would decrease the percentage of force produced in the early phase of muscle contraction (0-200 ms) and thereby impair the ability to react on sudden perturbations, potentially representing a functional deficiency in postural control and other types of reactive motor tasks (Pijnappels et al., 2008, Aagaard et al., 2010). Knowledge on these variables are important to fully understand muscle strength deficiencies in this population.

Altered neuromuscular activity/control and gait biomechanics have been observed in meniscectomized patients. Changes include increased KAM compared to controls (Sturnieks et al., 2008a, Sturnieks et al., 2008b), altered knee flexion and extension moments compared to controls (Bulgheroni et al., 2007), reduced ROM (Durand et al., 1993, Magyar et al., 2008, Sturnieks et al., 2008b), reduced cadence and walking speed (Durand et al., 1993), which was associated with reduced neuromuscular activity (Durand et al., 1993, Moffet et al., 1993). However, when interpreting these results with respect to knee OA development the same limitations apply as with studies on muscle strength (i.e. either a short follow-up time or studies with mixed populations – traumatic or degenerative tears, young/old patients). Therefore, it is difficult to interpret the potential influence of these results on knee OA development and more knowledge is needed to further understand the potential changes in neuromuscular activity and knee joint kinetics and kinematics in patients in a 'pre-osteoarthritis' state.

Aims of the thesis

General aim

To identify potential impairments in neuromuscular function and self-reported pain and function in middle-aged meniscectomized patients at high risk of knee OA.

Specific aims

1. To identify reductions in muscle strength, rapid force capacity and functional performance between the operated and contra-lateral leg of patients and compared with controls (paper I).

2. To assess level of self-reported pain and function in meniscectomized patients at high risk of knee OA compared to population-based controls (Paper I).

3. To identify differences in kinematic and kinetic variables and neuromuscular activity during a stair descent task between the operated and contra-lateral leg of patients and compared with controls (Paper II).

4. To investigate if changes in muscle strength, rapid force capacity and functional performance differ between the operated and contra-lateral leg of patients and compared with controls from 2 to 4 years post meniscectomy (Paper III).

Methods

Participants

A detailed overview of the baseline and follow-up recruitment flow is shown in Figure 4.

Paper I

Patients, 35-55 years old at the time of surgery, who had undergone surgery for a medial meniscus tear in the posterior half of the meniscus in the years 2006 and 2007 were identified for baseline assessment through the surgical code system from two different hospitals. The age criteria were set to include a majority of patients with degenerative meniscus tears but without knee OA. Patients were excluded if they were misclassified by the surgical code system, or if they had a previous knee ligament injury, severe cartilage changes defined as deep clefts or visible bone at meniscectomy, or self-reported co-morbidities limiting participation in the study. Following surgery patients were given a leaflet with standard rehabilitation exercises which they were encouraged to perform at home. Information on compliance with the exercise recommendation was not collected.

Age and gender matched controls were identified through the Danish Civil Registration System. An invitation was sent to a total of 600 people living in the same geographic area as the meniscectomized patients. Subjects were excluded if they had had a previous knee ligament injury, knee surgery or self-reported co-morbidities limiting participation in the study. Eligible controls were stratified into four groups: men 35-45, men 46-55, women 35-45, and women 46-55 years.

The intention was to include a control randomly selected from the appropriate age group by use of a random number generator for each patient included. Due to a slow recruitment process of patients in the beginning of the study, the first 7 controls were included before patients were included, which is the reason for the discrepancy between the number of women, 10 and 12, respectively, in the patient and control groups (Paper I). Therefore, the study was matched on a group level instead of on a case level.

At the initial baseline test session, 5 patients reported knee injuries in the contra-lateral knee (which had not been reported during the screening process): 3 patients had a meniscectomy, 1 patient had a deficient anterior cruciate ligament (ACL), and 1 patient had an ACL reconstruction and meniscectomy. These patients were not excluded since our a priori hypothesis was a bilateral strength deficit between patients and controls. Furthermore, their results in the strength and functional tests were within 2 SDs of the mean of contra-lateral leg. All other patients had a healthy control leg. Characteristics of participants included in paper I is shown in Table 1.

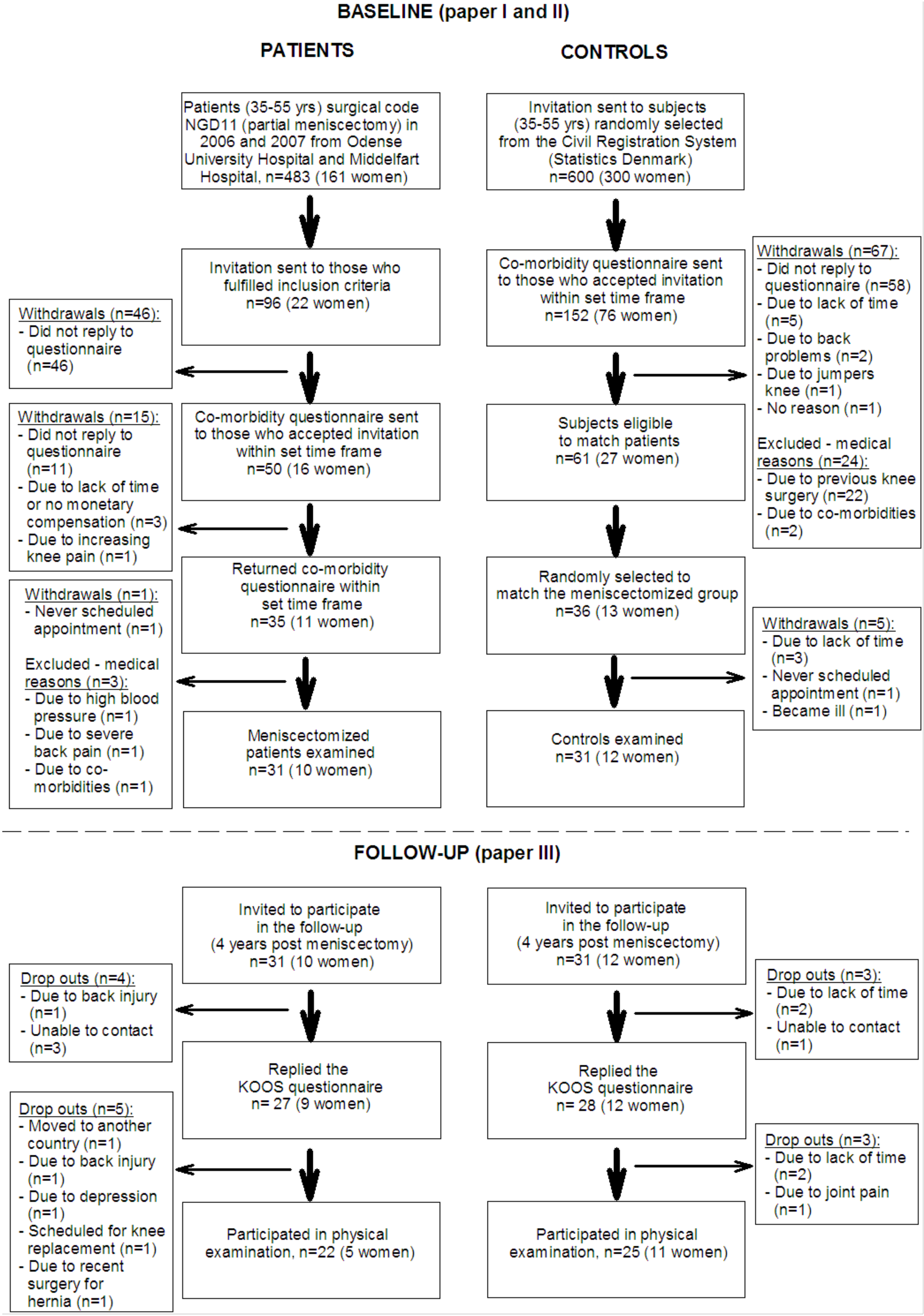

Figure 4: Flow-chart of the baseline and follow-up recruitment process of meniscectomized patients and controls

Paper II

Due to EMG equipment malfunction during the first baseline assessment on two consecutive testing days, 5 patients and 5 controls had to be excluded from paper II. Of the remaining 26 patients, four patients reported knee injuries to the contra-lateral knee. Due to the mechanistic focus of paper II these patients were also excluded. Characteristics of participants included in paper II is shown in Table 1.

Paper III

The follow-up assessment was conducted ~2 years after the first assessment (i.e. 49.6±5.0 months [mean±SD] after meniscectomy). All participants from the baseline assessment received a written invitation to participate in the follow-up (Figure 4). If participants failed to reply to the invitation they were contacted by phone. Four patients (2 men/2 women) and 3 controls (3 men) had dropped out at the follow-up examination (Patients: 1 due to back injury, 3 unable to contact; Controls: 2 due to lack of time, 1 unable to contact). Overall, no differences were observed in physical characteristics (age, BMI and aerobic power) of patients (n=4) and controls (n=3) that dropped out compared to those who were available for follow up at 4 years post meniscectomy. However, controls that dropped out demonstrated a higher hand grip strength (51.5±7.3 vs. 36.6±7.7 kg [mean±SD], p=0.003).

Furthermore, 5 patients (1 man/4 women) and 3 controls (2 men/1 woman) were only able/willing to reply the KOOS questionnaire and did not participate in the physical examination at the follow-up (Patients: 1 moved to another country, 1 due to back injury, 1 due to depression, 1 scheduled for knee replacement, 1 due to recent surgery for hernia; Controls: 2 due to lack of time, 1 due to joint pain). Characteristics of participants included in paper III is shown in Table 1.

Descriptive variables

Co-morbidities

A validated questionnaire (Sangha et al., 2003) was used to assess co-morbidities prior to inclusion of patients and controls. The questionnaire contains a list of several typical

Table 1: Baseline characteristics of study participants included in paper I, II and III. Time surgery = time since surgery, BMI = body mass index (body weight/height^2), Aerobic power = maximum oxygen uptake, Grip strength = hand grip strength, Co-morbidities = number of participants reporting co-morbidities (i.e. 1-2 musculoskeletal co-morbidities/1-2general co-morbidities). Musculoskeletal co-morbidities reported other than knee problems; joint problems, back pain. General co-morbidities reported; high blood pressure, diabetes, ulcer, heart problems, depression. Values are mean±SD or no.

Participants	Paper	N (no.)	Sex, % women	Time surgery (mth)	Age (yrs)	BMI (kg/m^2)	Aerobic power (ml $O_2 \cdot kg^{-1}$)	Grip strength (kg)	Co-morbidities (no.)
Patients	I	31	32	20.6±6.1	46.0±5.5	25.5±3.8	35.8±8.9	39.1±9.1	13/6
Controls	I	31	39	N/A	45.9±5.8	25.5±4.3	37.0±11.1	38.1±8.8	11/10
Patients	II	22	32	20.7±6.6	45.4±5.1	25.4±4.1	36.6±9.6	38.3±7.9	10/6
Controls	II	26	38	N/A	45.6±6.1	25.6±4.7	37.9±11.8	37.9±8.4	9/6
Patients	III	22	23	21.6±5.1*	46.6±5.0	24.7±2.9	37.9±8.2	41.4±7.8	10/3
Controls	III	25	44	N/A	46.4±5.2	25.1±4.6	35.9±9.5	36.7±7.4	8/7

*i.e. 49.6±5.0 month at follow-up

medical conditions (i.e. diabetes, heart disease, high blood pressure etc.). For each condition the participant is asked to indicate if they have the problem (yes/no), to indicate if they receive treatment for the problem (yes/no) and to answer if the problem limits their activities (yes/no). Patients and controls were included if the self-reported co-morbidities were treated and/or did not limit their activities or participation in the study.

Physical activity level

Physical activity level was reported at the baseline examination. Level of physical activity was reported as the amount (in hours and minutes) of vigorous and moderate physical activity undertaken during the previous 7 days and reported separately for work and leisure time. Each period of physical activity had to last for at least 10 minutes at a time. Vigorous physical activity was defined as activity that makes one breathe harder than normal, and moderate physical activity was defined as activity that makes one breathe somewhat harder than normal.

Hand grip strength

Maximal hand grip strength was measured at baseline using a handheld dynamometer (Smedlay's, Tokyo, Japan). Three trials were performed for the left and right hand, respectively. Participants were standing with their body straight and back against a wall with the elbow of the tested arm flexed to 90 degrees. Participants were instructed to gradually build up force and maintain maximal force for 2-3 s. During testing it was ensured that the elbow was not rested against the wall or the body of the subject to increase force output. The mean of the best trial for the left and right hand was reported.

Estimation of maximal oxygen consumption

Aerobic power was estimated from work load and heart rate during a sub-maximal bicycle warm-up prior to strength testing at the baseline examination using Åstrands Nomogram (Astrand and RYHMING, 1954). Participants were asked to cycle for 6 minutes while heart rate was recorded (Polar 610, Oulo, Finland). After 6 minutes heart rate was noted if it was between 120-170 beats pr min. (BPM) and stable during the prior 1-2 minutes. Otherwise the test was extended 1-2 minutes until heart rate was stable and between 120-170 BPM. Work load was adjusted to ensure a heart rate between 120-170 BPM after 6 minutes. Estimated maximal oxygen consumption was adjusted according to age prior to division with body mass to express maximal oxygen uptake as ml O_2 kg^{-1}.

Outcomes

For an overview of outcomes in papers I, II and III see Table 2. Informed consent form was signed at baseline and follow-up and the study procedures were approved by the ethics committee of the Region of Southern Denmark (ID: S-20080044). All procedures were identical at both examinations (i.e. baseline and follow-up) and the order of test-leg was randomized for both patients and controls (i.e. operated/contra-lateral and left/right, respectively).

Self-reported outcomes

The Knee injury and Osteoarthritis Outcomes Score (KOOS) (Paper I and III) is a knee-specific questionnaire to assess pain, symptoms, activities of daily living (ADL), activities during sport and recreation function (Sport/Rec) and quality of life (QOL) validated in patients with knee problems

(Roos et al., 1998a, Roos et al., 1998b). A normalized score is calculated for each subscale (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS has been validated for use in meniscectomized patients (Roos et al., 1998a). In the present thesis emphasis was on the subscales pain and Sport/Rec.

The Short Form-36 questionnaire (SF-36) (Paper I) is a generic, widely used measure of general health status (Ware, Jr. and Sherbourne, 1992). The SF-36 consists of 8 subscales; physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE) and mental health (MH). The SF-36 is self-explanatory, takes about 10 minutes to complete and is scored from 0-100 (0 indicating extreme problems and 100 indicating no problems). The Acute Danish version of the SF-36 was used (Bjorner et al., 1998a, Bjorner et al., 1998b).

Muscle strength assessment

At the baseline examination both isometric and dynamic muscle strength measurements were conducted (Paper I). At the follow-up examination only isometric measurements were performed (Paper III). All muscle strength tests were carried out in an isokinetic dynamometer (Kinetic Communicator 500H, Chattecx Corp., Hixson, TN, USA). Subjects were seated at a 10˚ reclining angle, e.g. slightly leaning back with 100˚ hip flexion with their arms folded over their chest and their body firmly strapped at the hip and thigh in an isokinetic dynamometer. The axis of rotation of the dynamometer lever arm was visually aligned to the axis of the lateral femoral epicondyle of the subject, and the lower leg was attached to the lever arm of the dynamometer 2 cm above the medial malleolus (Aagaard et al., 1998, Thorlund et al., 2008). The dynamometer force and position signals were recorded by a personal computer at a 1,000 Hz sampling rate during isometric tests and at a 100 Hz rate during dynamic tests, and was filtered by a fourth-order zero-lag Butterworth low-pass filter at 15 Hz cutoff frequency. To correct for the effect of gravity on the measured joint torques, the passive mass of the lower leg was measured in the dynamometer at a knee joint angle of 45° (Aagaard et al., 1995). In addition to the sub maximal bicycle warm-up, subjects performed a further warm-up and preconditioning exercise in the dynamometer, which consisted of several concentric and

Table 2: Overview of outcomes in paper I, II and III

	2 years post meniscectomy		4 years post meniscectomy
	Paper I	Paper II	Paper III
Maximal muscle strength	X		X
Rapid force capacity	X		X
One-leg hop for distance	X		X
Max. knee bends/30 s	X		X
Stair descent analysis		X	
KOOS	X		X
SF-36	X		

eccentric contractions, gradually increasing force. Maximal concentric, eccentric, and isometric muscle strength were measured unilaterally in the knee extensors and knee flexors in both legs of all participants. Knee joint angular velocity during dynamic testing was set to 30°/s with a knee joint range of motion from 90° to 20° (0° = full knee extension). Successive trials at each contraction mode were conducted until the subject was unable to further increase peak torque (4–6 trials were typically conducted). Isometric MVC was measured at a 70° knee joint angle (best of 3 trials) during knee extension and flexion, respectively. RFD was calculated as the average slope (Δ torque/Δ time) at time points 0–30, 50, 100, and 200 ms of the torque-time curve to evaluate the capacity for rapid force production. These time intervals have previously been used to assess RFD in the initial phase of muscle contraction in healthy subjects (Aagaard et al., 2002, Thorlund et al., 2008) and in surgical patients (Suetta et al., 2004). The onset of contraction was defined as the instant where force increased by 2% of peak torque above the resting baseline level. Visual feedback of the dynamometer torque output was provided to the subjects on a computer screen after each trial (Kellis and Baltzopoulos, 1996). The reliability and validity of the KinCom dynamometer have previously been verified in detail (Farrell and Richards, 1986, Sole et al., 2007).

Figure 5: One-leg hop test.

Functional capacity tests

The one-leg hop test (Paper I and III) (Tegner et al., 1986) was used to assess the longest distance that could be covered in a one-leg jump. The test has shown to be valid and reliable in middle-aged meniscectomized patients (Bremander et al., 2007). The subject was standing on one foot with the hands on the back and was asked to jump as far as possible and land steadily on the same foot. The subject has to be able to land and stand long enough for the examiner to measure the length of the jump. At least 3 trials with a 60 s rest period between each attempt (or until the subject made no further progress) were conducted, and the longest jump was recorded (Figure 5).

The maximum number of knee bends performed in 30 s (Paper I and III) (Roos et al., 2001) was also assessed. The test has shown to be valid and reliable in middle-aged meniscectomized patients (Bremander et al., 2007). The subject´s long axis of the foot was aligned with a straight line and the toes placed on a perpendicular line; light fingertip support was provided to the subject by the examiner to aid balance. The subject was asked to flex the knee while standing on one leg, without bending forward at the hip, until the line along the toes was no longer visible to the subject (~30° knee flexion). The maximum number of knee bends performed in 30 seconds was recorded (Figure 6).

Figure 6: Maximum number of knee bends test.

Stair descent analysis

A biomechanical analysis of stair descent based on synchronous force plate, EMG and goniometer recording was conducted, as it represents a challenging functional task in daily life (Figure 7). Subjects were asked to descend a 4-step staircase at a self-chosen speed, without the use of hand rails wearing their own comfortable walking shoes. At the bottom of the stairs subjects continued walking performing a horizontal transition step down onto a force plate imbedded in the floor. The horizontal staircase position was adjusted relative to the position of the force plate so that the length of the horizontal transition step corresponded to 1/3 of the total leg length for each individual subject (measured from the midpoint of the greater trochanter to the midpoint of the lateral malleolus). Subjects were carefully instructed to continue walking until they reached a cone placed 2 meters beyond the force plate. Subjects were allowed 2-3 stair descent trials for the purpose of familiarization prior to actual testing. Subsequently, two experimental trials were performed for each leg (i.e. the operated and contra-lateral for the patients and the left and the right leg of the controls) and the average of these two trials was used for further analysis. Trials were repeated if visible hesitation, misplaced footing, or stumbles were observed. The staircase was designed with a step height of 16 cm, a depth of 23 cm, and a width of 60 cm. In the current study experimental focus was on the transition step between stair descent and subsequent level walking, as this transition step involves high peak ground reaction forces (GRF_{peak}). In fact GRF at impact is considerably higher during this transition than during level gait, stair ascent and descent. Thus, the first part of foot strike during this transition step represents a daily task with high GRF and knee joint loading (Figure 8).

Knee angle recordings: Flexible electro-goniometers (Biometrics SG150, Biometrics Ltd., Gwent, UK) were placed laterally across both knees of the subjects according to the manufacturer's manual to measure instantaneous knee joint angle during movement. During later off-line analysis the instants of foot strike and toe-off were determined from the GRF curve and used as temporal reference points. The goniometer was calibrated with the knee flexed at a 90-

Figure 7: Stair descent test

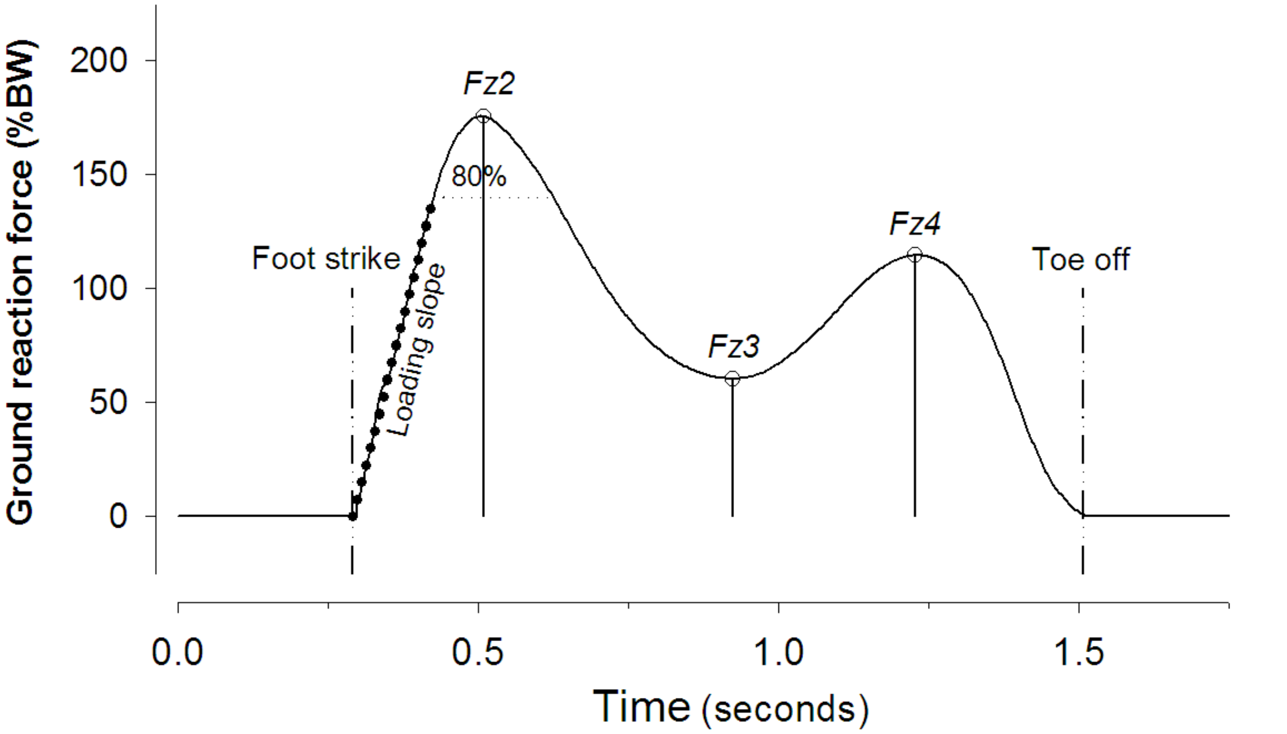

Figure 8: Example of the M-shaped GRF trajectory (*Fz* expressed in % of body weight) during the stance phase of the transition step between stair descent and horizontal walking. Variables are: *Fz2* – the first peak force (typically also GRF_{peak}), present in weight acceptance; *Fz3* – the minimum force, present during mid-stance and represents unloading; *Fz4* – the second peak force, present in the push-off phase prior to take-off (*Fz3* and *Fz4* was not analyzed in the present study).

degree angle (0 degrees = full extension).

Force plate analysis: The methods used for data collection and processing of ground reaction forces are similar to those reported by Larsen et al. (Larsen et al., 2008). In brief, a force plate (Kistler 9281 B, Winterthur, Switzerland) was placed in the floor at a distance of 1/3 the leg length of the subject from the final step of the stairs. The force plate was completely isolated from the staircase structure and the floor in order to avoid vibration artifacts. The vertical GRF signal (*Fz*) was recorded at 1000 Hz using a 12-bit A/D converter (DT 3010, Data Translation, Marlboro, MA, USA) (Larsen et al., 2008). Furthermore, two strain-gauge-based load cells connected to a custom-made amplifier were integrated in the second and fourth step of the stair case. The duration between contacts on the two load cells (steps) were determined from the on-off signals provided by the load cells and used to calculate stride frequency. In the current study, analytical focus was given to the first part of the *Fz* signal (Figure 8), which represents the vertical impact phase (i.e. weight acceptance) and thus comprises the phase of GRF_{peak} and energy absorption by the knee extensors during ground contact, being the phase most demanding for the knee joint. All *Fz* (GRF) signals were normalized as a percentage of body weight (%BW) and rate of GRF rise during the initial stance phase (loading slope: $Load_{slope}$) and the peak ground reaction force (GRF_{peak}) were calculated. GRF_{peak} occurred in the first half of the *Fz* signal (*Fz2*, Figure 8). In some cases an initial force peak (*Fz1*) was detected prior to *Fz2* and if higher than *Fz2*, *Fz1* was identified as GRF_{peak}. However, in most cases *Fz1* was lower than *Fz2*. $Load_{slope}$ was defined as the mean rate of *Fz* rise expressed in percentage of body weight (%BW s^{-1}) from the instant of foot-strike to 80% of GRF_{peak} and reflects the ability to absorb GRF impacts during the initial phase of foot contact. Furthermore, the stride frequency (strides/minute) (S_{freq}), average knee joint velocity (^{o} s^{-1}) from foot-strike to GRF_{peak} (V_{mean}), time from foot-strike to GRF_{peak} ($T_{peakGRF}$) and time for the entire stance phase (T_{stance}) were determined.

Electromyography (EMG) recording and analysis: Bipolar surface EMG signals were obtained during stair descent from selected knee extensor and flexor muscles (vastus lateralis: VL; vastus medialis: VM; biceps femoris: BF and semitendinosus: ST) and were subsequently normalized to the maximal EMG signal amplitude recorded during an isometric maximal voluntary contraction (MVC). Three MVC trials for the quadriceps and hamstring muscles, respectively, were conducted following the stair descent tests. The MVCs were performed in a sitting position as maximal isometric extensor or flexor contractions, respectively. The hip was flexed at 90 degrees and the knee angle was in 60 degrees extension. Strong verbal encouragement was given during every contraction to promote maximal voluntary effort.

EMG signals were obtained according to procedures previously used in our laboratory (Thorlund et al., 2008, Larsen et al., 2008) and in agreement with SENIAM recommendations (www.SENIAM.org) using pairs of Ag/AgCl surface electrodes, (Ambu, Blue Sensor M, M-00-S/50, Ballerup, Denmark) with a 20 mm inter-electrode distance. Before placing the electrodes, the skin was shaved and cleaned with alcohol to reduce electrode-skin impedance. EMG electrodes were directly connected to small custom-built preamplifiers taped to the skin. The EMG signals were transmitted through shielded wires to a custom-built differential instrumentation amplifier with a frequency response of 10–10,000 Hz and a common mode rejection ratio > 100 dB. An amplifier gain of 400 (=52 dB) was used, and included analogue high-pass (10 Hz) and low-pass filtering (550 Hz), respectively. Signal-to-noise ratio exceeded 55 dB (Thorlund et al., 2008, Larsen et al., 2008).

All EMG signals were synchronously sampled at a 1000 Hz sampling rate along with the goniometer and force plate signals. During subsequent analysis, any potential DC offset was removed from the raw EMG signals by linear de-trending and subsequently the signals were digitally high-pass filtered at 5 Hz cut-off frequency, followed by full-wave rectification and low-pass filtering at 10 Hz cut-off frequency (Aagaard et al., 2000). All filtering routines used fourth-order zero-lag Butterworth filters. Finally, all EMG signals were normalized to their peak EMG amplitude during MVC.

Neuromuscular activity was calculated as the mean normalized EMG amplitude during the loading slope phase (Act_{load}) and at peak GRF ($Act_{peakGRF}$; mean in a 20 ms time interval prior to the instant of GRF_{peak}). As described by Larsen et al. (Larsen et al., 2008), the magnitude of agonist-antagonist muscle co-activation was calculated as the magnitude of relative normalized signal-overlapping (common EMG-signal area) for two EMG signals: EMG_a and EMG_b expressed relative to the total EMG signal area calculated in a given time interval.

$$\text{Co} - \text{activation} = \frac{\int \min\{EMG_a, EMG_b\}\, dt}{\int \max\{EMG_a, EMG_b\}\, dt}$$

Muscle co-activation was calculated for the whole thigh (mean knee extensor activity vs. flexor activity) and separately for the lateral and medial thigh muscle, respectively, during the loading slope phase (Co-act_{load}: from the instant of foot strike to 80% GRF_{peak}) and at peak GRF (Co-$act_{peakGRF}$; mean in the 20 ms time interval prior to the instant of GRF_{peak}). Additionally, to investigate the distribution of overall medial vs. lateral muscle activity, mean medial ((VM+ST)/2) and mean lateral ((VL+BF)/2) neuromuscular activity were also calculated, in the operated and contra-lateral leg of the patients and for the left/right leg of the controls during the initial weight acceptance phase (loading slope phase) and at GRF_{peak} (mean in the 20 ms time interval prior to the instant of GRF_{peak}).

Statistics

Sample size calculation

Becker et al. (Becker et al., 2004) has previously reported a ~20% difference in quadriceps MVC between meniscectomized patients and controls. Our sample size calculation indicated a need for 25 individuals in each group to detect a similar difference in quadriceps MVC at the baseline examination (power=0.80, significance level=0.05).

Basic statistics

Students unpaired t-test, chi^2-test and the Mann-Whitney test were used to compare subject characteristics between patients and controls as appropriate (Paper I, II and III). Furthermore, the students paired t-test was used to evaluate differences between medial vs. lateral muscle activity within the different legs (i.e. operated, contra-lateral and control legs) (Paper II) and the Mann-Whitney test was used to compare self-reported outcomes between patients and controls (paper I and III). Correlation analyses were performed by calculation of Spearman´s Rho to assess the relationship between KOOS Sport/Rec and various strength variables (Paper I). Furthermore, to examine the relationship between the magnitude of self-reported pain in patients and those kinetic, kinematic and EMG outcome variables obtained in the operated leg that were significantly different from those of the contra-lateral leg or control legs (Paper II).

Multivariate statistics

Mixed linear random effects models (Rabe-Hesketh and Skrondal, 2008) were used to evaluate differences in outcome variables between operated legs, contra-lateral legs and control legs of patients and controls, respectively.

Paper I: To assess differences in strength and functional performance variables a mixed linear model was used with ‘subject’ as random effect and ‘leg’ (i.e. operated, contra-lateral and control legs) as fixed effect. Differences between legs in torque-time curve pattern (and hence RFD) were also assessed by using a mixed linear model with the combination of ‘subject’ and ‘side’ (i.e. repeated nested measurements on each leg of the subjects) as random effects and ‘leg’ (i.e. operated, contra-lateral and control legs) and ‘time point’ (i.e. 0-30, 50, 100 and 200 ms) as fixed effects. In all models age and sex were introduced as covariates to adjust for potential confounding, as anticipated in classical epidemiology.

Paper II: A mixed linear model was used to evaluate differences between legs in the kinematic, kinetic and EMG variables of interest with ‘subject’ as random effect and ‘leg’ as fixed effect. If data did not follow the Gaussian distribution, they were log-transformed prior to analysis, although data are still presented as non-log transformed means.

Paper III: To assess differences in change in maximal knee extensor/flexor MVC and functional performance a mixed linear model with ‘subject’ as random effect and ‘leg’ as fixed effect was used. Furthermore, changes in RFD at 0-30, 50, 100 and 200 ms were also assessed by using a mixed linear model with the combination of ‘subject’ and ‘side’ (i.e. repeated nested measurements on each leg of the subjects) as random effects and ‘leg’ (i.e. operated, contra-lateral and control legs) as fixed effect. All models were adjusted for values at baseline assessment, age and sex.

Stata 10.1 (Statacorp, College Station, TX, USA) were used for all statistical analyses, with a pre-specified level of significance = 0.05.

Results

Maximal muscle strength, rapid force capacity and functional performance

Overall, no differences were observed between the operated and contra-lateral legs of patients or when compared with controls in any of the strength variables or in functional performance at the baseline assessment 2 years post meniscectomy (Table 3). Furthermore, no differences were observed in rapid force capacity (i.e. no right shift in the torque-time curve and hence no reduction in RFD) during maximal isometric knee extension (p=0.18) (Figure 9) and knee flexion (p=0.71) at baseline.

At the follow-up examination 4 years post meniscectomy no differences in change were observed between the operated, contra-lateral and control legs in knee flexor MVC, functional performance (Table 4) or overall knee extensor or flexor RFD (p>0.10 and p>0.34, respectively) from baseline to follow-up. A tendency towards a difference in change in knee extensor MVC was observed from baseline to follow-up between the operated, contra-lateral and control legs (Table 4). Post-hoc analysis showed a significant difference in change in knee extensor MVC (p=0.04) from baseline to follow-up when comparing only the operated and contra-lateral leg.

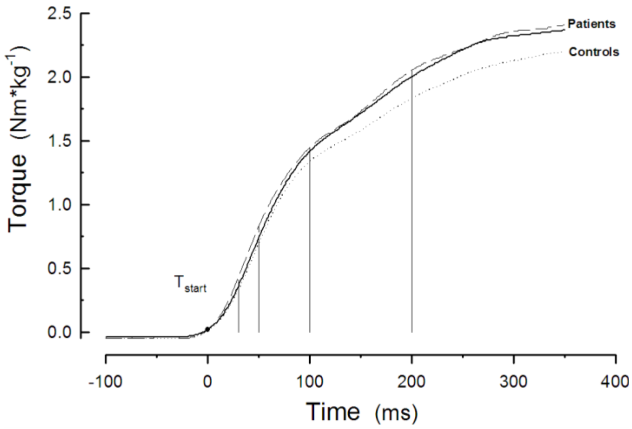

Figure 9: Mean torque time curve during knee extension for the operated leg (solid line, n=29), contra-lateral leg (dashed line, n=29), and control legs (dotted line, n=31 [62 legs]). No difference in rapid force capacity using the time points 0–30, 50, 100, and 200 ms were observed between any of the legs (mixed linear model).

Table 3: Isokinetic muscle strength and functional performance at the baseline examination (2 years post meniscectomy). Values are means adjusted for age and sex with 95% confidence intervals. Mixed linear model. P-value indicate main effect of "leg". n=29 patients in isokinetic tests (one patient failed to meet for the second test and, one patient did not complete the isokinetic strength test due to severe pain after the warm-up procedure).

	Patients			
	Operated leg (n=31)	**Contra-lateral leg (n=31)**	**Controls (n=31, 62 legs)**	***p*-value**
ISOKINETIC MUSCLE STRENGTH				
Knee extension				
Concentric peak torque (Nm kg^{-1})	2.66 (2.50-2.82)	2.73 (2.57-2.89)	2.55 (2.40-2.70)	0.20
Eccentric peak torque (Nm kg^{-1})	3.37 (3.13-3.61)	3.48 (3.24-3.72)	3.27 (3.05-3.48)	0.29
Isometric MVC (Nm kg^{-1})	2.80 (2.62-2.99)	2.88 (2.70-3.08)	2.70 (2.54-2.87)	0.26
Knee flexion				
Concentric peak torque (Nm kg^{-1})	1.37 (1.28-1.47)	1.39 (1.30-1.48)	1.39 (1.31-1.47)	0.84
Eccentric peak torque (Nm kg^{-1})	1.76 (1.62-1.89)	1.79 (1.65-1.92)	1.87 (1.74-1.99)	0.46
Isometric MVC (Nm kg^{-1})	1.20 (1.10-1.30)	1.26 (1.17-1.36)	1.20 (1.11-1.29)	0.23
FUNCTIONAL PERFORMANCE				
Max. no. knee bends / 30 s (no.)	25.8 (22.3-29.3)	26.1 (22.6-29.6)	28.6 (25.2-32.1)	0.45
One-leg hop (cm)	82.4 (73.6-91.1)	84.5 (75.7-93.3)	91.1 (82.6-99.6)	0.27

Stair descent performance

Kinematic and kinetic variables

No differences were observed between patients and controls in knee ROM, movement speed and GRF variables. However, patients showed a reduced stance phase (T_{stance}) when stepping out on the operated leg compared to the contra-lateral leg (post-hoc test, p=0.01). In support, there was a tendency for increased stride frequency (S_{freq}) in trials where patients performed the stair descent transition step using the operated leg compared to the contra-lateral leg (Table 5).

Neuromuscular activity

No differences were observed in level of activation between the operated, contra-lateral and control legs (Paper II). Patients and controls displayed less activity in the medial hamstring muscle (ST) compared to the lateral (BF) hamstrings during the stair descent task. Furthermore, patients showed increased medial (VM) vs. lateral (VL) knee extensor activity at peak GRF ($Act_{peakGRF}$) in the contra-lateral leg ($p \leq 0.05$), along with a tendency towards reduced medial (VM) vs. lateral activity (VL) in the operated leg compared to the contra-lateral leg (Paper II). No differences in medial vs. lateral knee extensor activity were observed in controls.

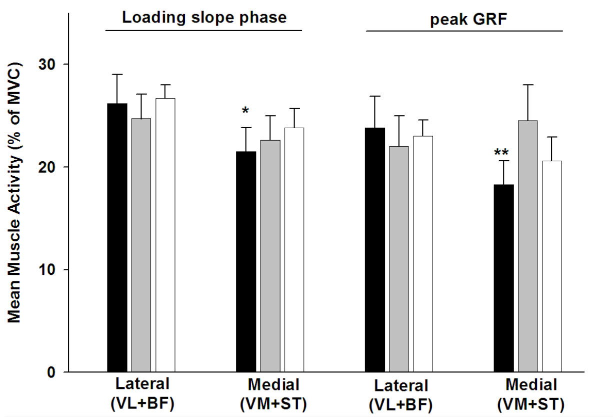

Figure 10: Lateral (VL+BF) vs. medial (VM+ST) mean muscle activity for the operated leg (black bars) and contra-lateral leg (grey bars) of the patients (n=22) and control legs (n=26, 52 legs) (white bars) during initial weight acceptance (loading slope phase) and at GRF_{peak} (mean in preceding 20 ms time interval). Values are means ± SE. Significant difference compared with mean lateral muscle activity, * $p \leq 0.05$, ** $p \leq 0.01$.

The magnitude of muscle co-activation was similar in patients and controls. However, controls showed a tendency to an elevated level of co-activation compared to patients for the medial thigh muscles during the loading

Table 4: Maximal muscle strength and functional performance at baseline (2 years post meniscectomy) and change from baseline to follow-up (4 years post meniscectomy) for the operated leg (n=22), contra-lateral leg (n=22) and control legs (50 legs, n=25). P-value indicate main effect of "leg".

	Baseline, Un-adjusted mean (SD)				**Change from baseline assessment, Mean adjusted for baseline, age and sex (95% CI)**			
	Operated leg	Contra-lateral leg	Control leg	*p*-value	Operated leg	Contra-lateral leg	Control leg	*p*-value
Knee extensor MVC (Nm kg^{-1})	2.91 (0.60)	2.93 (0.54)	2.60 (0.43)	0.13	0.01 (-0.16-0.18)	0.19 (0.02-0.37)	0.04 (-0.10-0.18)	0.09
Knee Flexor MVC (Nm kg^{-1})	1.20 (0.21)	1.27 (0.23)	1.18 (0.28)	0.27	0.06 (-0.02-0.14)	0.06 (-0.02-0.15)	0.05 (-0.02-0.12)	0.95
Knee bends/ 30 s (no.)	27.2 (9.6)	26.9 (8.4)	29.8 (10.8)	0.50	5.0 (2.7-7.3)	4.0 (1.8-6.3)	3.9 (1.8-6.0)	0.22
One-leg hop (cm)	92.4 (20.0)	91.5 (19.7)	90.5 (23.4)	0.92	3.5 (-1.9-9.0)	5.3 (-0.2-10.8)	-0.8 (-5.4-3.7)	0.25

slope phase (Paper II).

No differences were observed in mean medial (VM+ST) vs. mean lateral (VL+BF) muscle activity between the operated, contra-lateral leg and control legs (Figure 10). However, in meniscectomized legs**,** the mean neuromuscular activity was lower in the medial compared with the lateral thigh muscles during the loading slope phase ($p \leq 0.05$) and at GRF_{peak} ($p \leq 0.01$) (Figure 10). In contrast, no medio-lateral differences in overall thigh muscle activity were observed for the contra-lateral leg or in control legs (Figure 10).

Self-reported outcomes

At the baseline examination two years post meniscectomy patients self-reported worse knee related function than controls in the KOOS sub scales ADL ($p \leq 0.001$) and Sport/Rec ($p \leq 0.001$), as well as worse general physical function (PF) score on the SF-36 sub scale ($p \leq 0.001$). Additionally, patients reported more knee pain ($p \leq 0.001$), bodily pain (SF-36, paper I, $p \leq 0.01$), other knee symptoms ($p \leq 0.001$), and worse knee related quality of life scores ($p \leq 0.001$) than controls (Figure 11).

In addition to the drop-outs from baseline to follow-up (i.e. 4 patients and 3 controls) 5 patients and 3 controls (for more details see Methods section) were only able/willing to reply to the KOOS questionnaire and did not participate in the physical examination at follow-up. Patients that only answered the questionnaire (n=5) self-reported more pain (p=0.03), more symptoms (p=0.004), impaired ADL (p=0.03) and reduced Sport/Rec function (p=0.01) together with a tendency towards reduced QOL (p=0.08) than patients completing the 4 year follow up (n=22). In contrast, there were no difference in any KOOS subscale scores between

Table 5: Kinematic and kinetic variables during the transition step from stair descent to level walking at 2 years post meniscectomy. Values are mean with 95% confidence intervals. Mixed linear model. P-value indicates main effect of "leg". Knee angle at foot-strike ($Angle_{foot\text{-}strike}$), knee angle at toe-off ($Angle_{toe\text{-}off}$), range of motion during stance phase (ROM_{stance} – difference between knee angle foot-strike and toe-off), range of motion during weight acceptance (ROM_{weight} – difference between knee angle foot-strike and maximal knee flexion during weight acceptance), stride frequency (S_{freq}), mean knee angular velocity from foot-strike to peak GRF (Vmean), time foot-strike to peak GRF ($T_{peakGRF}$), time entire stance phase (T_{stance}), peak GRF (GRF_{peak}), loading slope ($Load_{slope}$).

	Patients			
	Operated leg (n=22)	**Contra-lateral leg (n=22)**	**Controls (n=26, 52 legs)**	***p*-value**
KNEE JOINT POSITION				
$Angle_{foot\text{-}strike}$ (°)	11.5 (8.5-14.5)	11.4 (8.4-14.4)	10.4 (8.1-12.6)	0.82
$Angle_{toe\text{-}off}$ (°)	54.3 (51.7-57.0)	55.8 (53.1-55.4)	53.7 (51.8-55.7)	0.44
ROM_{stance} (°)	42.9 (40.6-45.1)	44.3 (42.1-46.6)	43.4 (41.6-45.1)	0.42
ROM_{weight} (°)	20.8 (18.8-22.7)	22.4 (20.5-24.4)	21.2 (19.7-22.7)	0.22
MOVEMENT SPEED				
S_{freq} (stride/min)	68.0 (62.5-73.5)	65.7 (60.1-71.2)	61.6 (56.7-66.5)	0.07
V_{mean} (° s^{-1})	130.1 (110.4-149.7)	148.5 (128.8-168.1)	138.5 (123.9-153.1)	0.26
$T_{peakGRF}$ (ms)	109.4 (96.3-122.5)	107.8 (94.7-120.9)	106.8 (96.3-117.2)	0.94
T_{stance} (ms)	*657 (615-699)	679 (637-721)	677 (640-715)	0.04
GROUND REACTION FORCES				
GRF_{peak} (%BW)	163.4 (154.1-172.7)	169.8 (160.5-179.1)	160.3 (152.4-168.2)	0.12
$Load_{slope}$ (%BW s^{-1})	1966 (1650-2283)	2135 (1818-2451)	1904 (1636-2172)	0.32

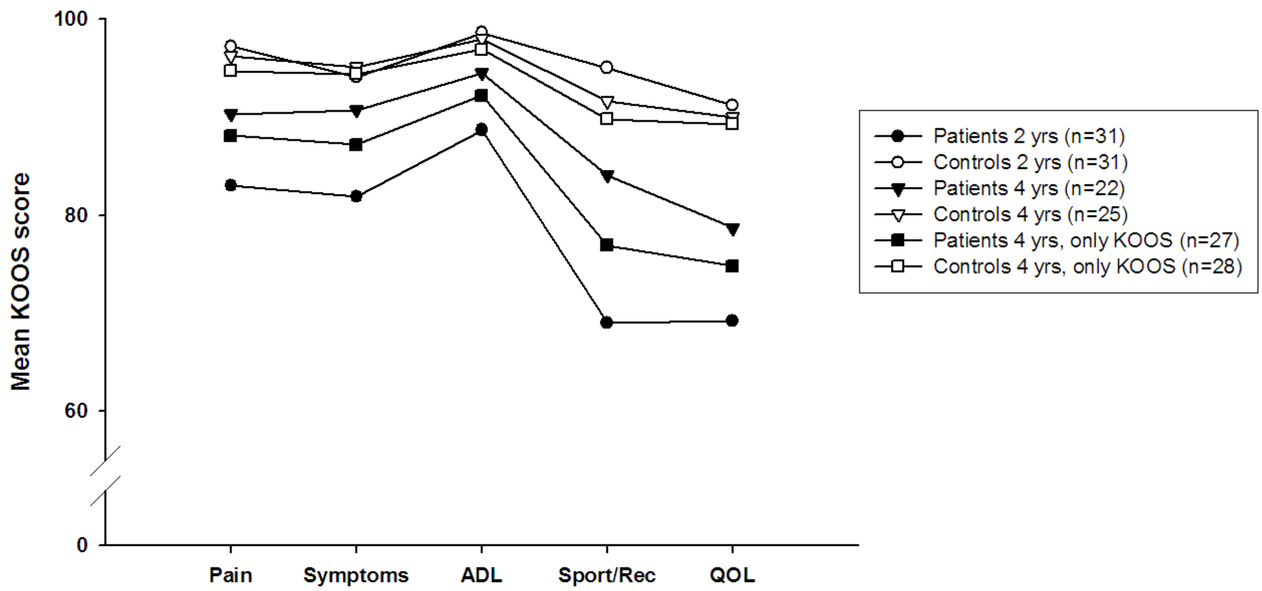

Figure 11: Knee Injury and Osteoarthritis Outcome Score (KOOS) results at baseline (2 years post meniscectomy) (indicated by circles) and at follow-up (4 years post meniscectomy) (triangle indicate subjects with full data set and square indicate data including participants only replying the KOOS questionnaire) for the patients (solid markers) and controls (open markers). Scores are means presented as an outcome profile of the 5 dimensions of the KOOS scale, where a score of 100 represents no knee problems and a score of 0 represents extreme problems. ADL=activities of daily living; Sport/Rec=sports and recreational function; QOL=quality of life.

controls participating in the physical examination (n=25) and controls who only replied the questionnaire (n=3). KOOS scores are presented at 2 and 4 years for patients and controls participating in the full examination and including patients and controls only replying to questionnaire at follow-up (squared symbols, Figure 11).

Patients participating in the full follow-up examination 4 years post meniscectomy self-reported reduced knee related QOL compared with controls (p=0.007). Furthermore, tendencies towards patients reporting more pain (p=0.08) and symptoms (p=0.08) compared to controls were observed at follow-up. No differences were evident in ADL (p=0.18) or Sport/Rec (p=0.32) (Figure 11).

Discussion

Main findings

This thesis is based on the results of 3 studies (paper I, II and III) investigating neuromuscular function and self-reported pain and function in meniscectomized patients at high risk of knee OA.

Despite patients self-reporting pain and functional limitations no impairments in muscle strength and functional performance were observed between the operated and contra-lateral leg of patients or when compared with population-based controls 2 years after resection of a degenerative meniscus tear (paper I). However, minor alterations in kinematics and neuromuscular activity pattern were observed at 2 years post meniscectomy during stair descent between the operated and contra-lateral leg of patients (paper II). Furthermore, a difference in maximal knee extensor strength seemed to emerge over a 2 year period between the operated and contra-lateral leg of patients (paper III).

Neuromuscular function

Previous knee injury and impaired neuromuscular function are considered risk factors for knee osteoarthritis (OA) (Lohmander et al., 2007, Bennell et al., 2008). This thesis investigated different aspects of neuromuscular function in meniscectomized patients considered to represent a "pre-osteoarthritis" state (Englund et al., 2003, Becker et al., 2004, Englund and Lohmander, 2006). Some previous studies have reported quadriceps strength deficiencies (Stam et al., 1992, Gapeyeva et al., 2000), whereas others observed no difference in muscle function (St-Pierre et al., 1992, Stam et al., 1993, Matthews and St-Pierre, 1996) comparing the operated with the contra-lateral leg in meniscectomized patients. Furthermore, a number of studies have been conducted to investigate alterations in neuromuscular activity (Durand et al., 1993, Moffet et al., 1993, Magyar et al., 2008, Glatthorn et al., 2010) and changes in gait and stair ascent/descent biomechanics in meniscectomized patients (Durand et al., 1993, Moffet et al., 1993, Bulgheroni et al., 2007, Magyar et al., 2008, Sturnieks et al., 2008a, Sturnieks et al., 2008b). However, in the majority of studies investigating various aspects of neuromuscular function and biomechanical changes in meniscectomized patients, study populations have been rather heterogeneous including patients with different combinations of medial/lateral and traumatic/degenerative meniscus tears complicating the interpretation. Furthermore, the short-term recovery period investigated in the majority of studies may primarily represent recovery from the surgery-induced trauma rather than the meniscus tear *per se*.

Muscle strength and functional performance

In two recent studies investigating strength deficiencies 4 years after meniscectomy in patients similar to those in the present thesis, impaired knee extensor strength and functional capacity were observed in the operated compared with the contra-lateral leg (Ericsson et al., 2006) and bilaterally compared with controls (Becker et al., 2004). Paper I was designed to combine the strength of these two studies, by elucidating detailed aspects of muscle strength and functional performance impairments in meniscectomized patients compared with age- and gender-matched controls, and relating this to self-reported knee function. Unexpectedly however, the initial hypothesis of bilateral strength deficiencies between patients and controls could not be verified at 2 years post meniscectomy. Further, no differences were detected between the operated and contra-lateral leg of meniscectomized patients in maximal thigh muscle strength and functional performance tests. At baseline (paper I), patients were examined about 21 months after meniscectomy, whereas patients were examined about 48 months post meniscectomy in the studies by Becker et al. (Becker et al., 2004) and Ericsson et al.

(Ericsson et al., 2006) (Table 6). Thus, the discrepancies in muscle strength deficits between studies may be explained by the different post-surgery time intervals since the potential development of knee OA may not have progressed in the patients at 2 compared to at 4 years post meniscectomy.

To investigate this hypothesis a follow-up study was conducted 4 years post meniscectomy to investigate longitudinal changes in muscle strength and functional performance over 2 years time. No differences were observed in changes from

Table 6: Overview of studies investigating neuromuscular function in patients meniscectomized for degenerative tears.

	Becker et al. 2004	Ericsson et al. 2006	Thorlund et al. 2010 (Paper I)	Thorlund et al. (Paper III)
PATIENTS				
Age (yrs)	42.8 (7.9)	45.7 (3.2)	46.0 (5.5)	49.6 (4.8)
BMI (kg/m^2)	24.9 (2.9)	26.5 (3.3)	25.5 (3.8)	24.7 (2.7)
Men/women (no.)	32/0	29/16	21/10	17/5
Time since surgery, (mth)	48 (9)	48 (16)	20.6 (6.1)	49.6 (5.0)
Type of tear	APM of tear in the posterior part of the medial meniscus	APM	APM of tear in the posterior part of the medial meniscus	APM of tear in the posterior part of the medial meniscus
Recruitment (setting)	Not specified	Indentified through surgical code system	Indentified through surgical code system	From Thorlund et al. 2010
Physical activity level	No participation in sporting activities on regular basis	Excluded if no not able to walk outdoors. 30 patients had high activity level (hiking, biking etc.), 15 had low activity level (i.e. yard work, shopping etc.)	Moderately physically active during leisure time equivalent to controls	N/A
CONTROLS				
Age	40.8 (13)	-	45.9 (5.8)	49.4 (5.2)
BMI	25.6 (3.9)	-	25.5 (4.3)	25.2 (4.9)
Men/women	32/0	-	19/12	14/11
Recruitment (setting)	Not specified	-	Randomly chosen from the Danish Civil Registration system	From Thorlund et al. 2010
Physical activity level	Not specified	-	Moderately physically active during leisure time equivalent to patients	N/A
KNEE EXTENSOR DEFICITS				
Operated leg vs. contra-lateral leg	0 %	6-9 %	0 %	6 %
Operated leg vs. controls	~20 %	-	0 %	0 %

baseline to follow-up in maximal knee flexor muscle strength, overall knee extensor and flexor rapid force capacity (i.e. RFD) or functional performance between the operated and contra-lateral leg of patients or compared with controls. However, a tendency towards a difference in change in knee extensor MVC from baseline to follow-up was observed between the operated, contra-lateral and control legs (p=0.09). Post-hoc analysis showed a significant difference (p=0.04) in change in knee extensor MVC from baseline to follow-up resulting in a 6% difference between the operated and contra-lateral leg of patients at follow-up. This finding is in line with the findings by Ericsson et al. (Ericsson et al., 2006) reporting differences of 6-9% in peak knee extensor torque between the operated and contra-lateral leg. In contrast, Becker et al. (Becker et al., 2004) reported a bilateral strength deficit >20% between meniscectomized patients and controls. This discrepancy may be due to differences in patient selection, selection of controls and/or methodological differences.

In fact, patient recruitment *per se* could be suspected to be a major reason for the divergent results. Patient recruitment from a clinical setting or advertising for patients may introduce selection bias towards patients with more symptoms. In the present study, great care was taken during the recruitment process to ensure that patients were representative of a population of patients meniscectomized for a degenerative tears. Furthermore, the meniscectomized patients in the present study were very similar to controls at baseline except for the self-reported knee problems (paper I and Table 6). In the study by Becker et al. (Becker et al., 2004) none of the patients participated in sports activities and no information on participation in sports was given for the controls (Table 6). Thus, the reported difference between the patients and controls (Becker et al., 2004) might be influenced by a higher level of physical activity in the control group. In the current study, patients self-reported more moderate and vigorous physical activity at work than controls at baseline whereas physical activity during leisure time was equal in the patient and control group (paper I). However, general muscle strength (grip strength) and general fitness (aerobic power) were equal in patients and controls supporting similar physical activity levels (Table 1). Further, in the present study, controls were not excluded if they had minor self-reported co-morbidities that were similar to those of the patients, since this was to be expected in a population of middle-aged individuals. No information was given on co-morbid conditions in the study by Becker et al. (Becker et al., 2004), and thus it is not possible to know if different levels of co-morbidities between the studies could help explain the inconsistent results.

Relating the results from the present thesis to the existing body of literature on muscle strength deficits in patients undergoing meniscectomy a pattern seems to emerge (i.e. disregarding the discrepancies in patient age, type of tear and method of assessment). It seems that patients scheduled for meniscectomy experience some deficits in muscle strength already prior to surgery, which are exacerbated following meniscectomy likely due to the trauma and/or period of disuse/unloading associated with the surgery (Figure 12). This is followed by a second recovery phase (6-24 months) where full recovery seems to be reached at some point in time. The results from the present

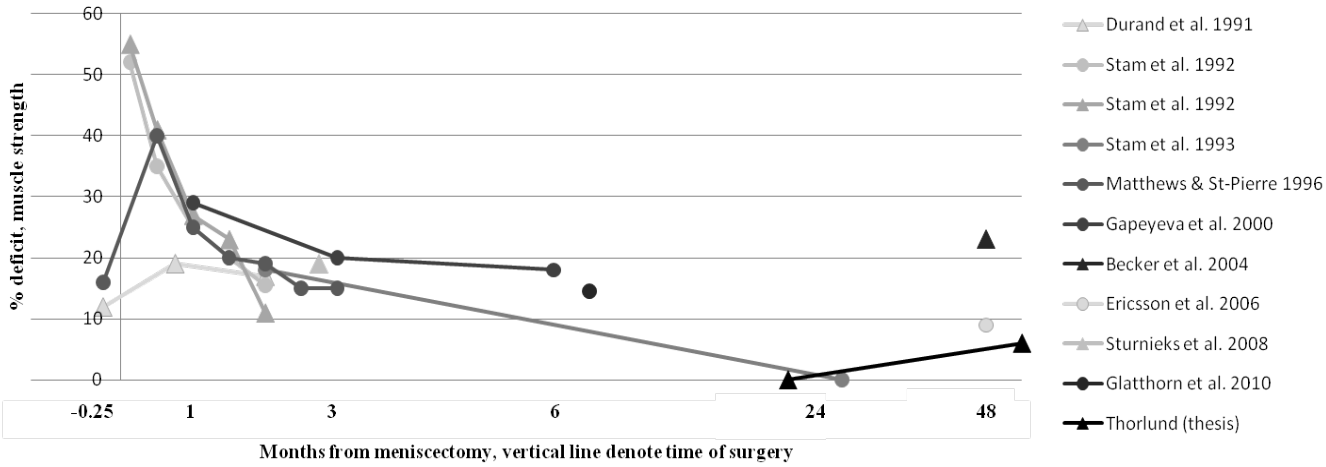

Figure 12: Overview of studies on muscle strength deficits in meniscectomized patients including the results of the present thesis. Age of patients, type of meniscus tear and method of muscle strength assessment vary between studies. Triangle denote comparison of meniscectomized leg to a control group, circle denote comparison to the contra-lateral leg. Studies with connecting lines indicate longitudinal data.

thesis together with the data by Becker et al. and Ericsson et al. (Becker et al., 2004, Ericsson et al., 2006) suggest that a third phase might occur where strength deficits start to evolve again (Figure 12). This proposed third phase of decline in muscle strength may be a window of opportunity for knee OA prevention strategies. However, this proposed time-course of muscle strength deficits in meniscectomized patients needs to be confirmed in prospective longitudinal studies.

Stair descent performance

In the present thesis (paper II) stair descent was used as a model to represent a demanding complex daily locomotor task with multiple degrees of freedom, in order to investigate potential changes in neuromuscular activation and knee joint kinetics/kinematics in patients at high risk of knee OA. Contrary to our expectations, no differences were observed in knee joint kinetics and kinematics between patients and controls. Likewise, no differences emerged in knee ROM, knee joint position or ground reaction force profile between the operated and contra-lateral legs of the patients. Nevertheless, a 3% reduction in the duration of the stance phase (T_{stance}) was observed in operated legs compared with the contra-lateral legs of patients potentially reflecting a greater reliance on the contra-lateral limb during stair descent. Further, we found that the duration of the stance phase (T_{stance}) on the operated leg was negatively related to self-reported knee pain (i.e. more pain was associated with a longer stance phase) (r_s=-0.47, p=0.03, paper II). This indicates that patients use a strategy where they produce a given amount of kinetic impulse (momentum) using an extended time of contact (t), which potentially may serve to reduce the magnitude of contact force [F] exerted in the knee joint [since Δmomentum = F · t] as a strategy to minimize pain during stair descent.

Neuromuscular activity was generally lower (~50%) in the medial (ST) vs. lateral (BF) hamstring muscles in the phases of interest in both legs of the patients. A similar pattern was observed in controls (~40% lower medial activity) indicating that this represents a general and normal pattern of hamstring activity during stair descent (paper II). Clinicians often report medial quadriceps (VM) atrophy and neuromuscular deficits following knee injury and delayed VM vs. VL muscle activity onset has been reported in patients with patellofemoral pain (Chester et al., 2008). Our results seems to support this notion since neuromuscular activity tended to be lower in the medial (VM) compared with the lateral (VL) quadriceps muscle in the operated leg of patients at the instant of GRF_{peak}.

Overall medial vs. lateral muscle activity was also investigated since skewed patterns of medial vs. lateral muscle activity could potentially affect knee control/function and joint stability. No differences were observed between mean medial (VM+ST) and mean lateral (VL+BF) muscle activity between the operated, contra-lateral and control legs. However, we observed reduced (~20%) medial compared with lateral mean muscle activity in the operated leg of patients. In contrast, no differences in medial vs. lateral muscle activity were observed in the contra-lateral leg of patients or in controls. Increased levels of lateral muscle activity have previously been observed in patients with knee OA compared with controls (Hubley-Kozey et al., 2006, Heiden et al., 2009), increasing with OA severity (Hubley-Kozey et al., 2009). This may represent a neuromuscular strategy to reduce knee adduction moment and decrease medial knee joint compartment loading (Heiden et al., 2009). Thus, the reduction in medial muscle activity currently observed in meniscectomized legs could reflect a strategy to decrease compression forces in the medial compartment of the knee joint. The specific impact of attenuated medial muscle activity on biomechanical knee joint loading profile and specifically on the knee adduction moment which is often used as a surrogate measure for medial knee compartment joint loading (Schipplein and Andriacchi, 1991, Noyes et al., 1992, Zhao et al., 2007) and is associated with medial knee OA severity (Sharma et al., 1998) currently remains unknown. Recently, Netravali et al. (Netravali et al., 2010) reported that patients meniscectomized for medial meniscus tears in the posterior part of the meniscus (similar to the present patients) showed increased external rotation of the tibia throughout the stance phase during walking. The presence of such a gait pattern is likely to affect knee joint stability and could be an alternative explanation for the altered medial vs. lateral muscle activity in the meniscectomized legs observed in the present thesis.

It was expected that meniscectomized patients would demonstrate altered patterns of neuromuscular control including increased muscle co-activation which have been suggested to be responsible for the reduced knee ROM seen in patients with knee OA. However, we did not observe any reductions in patient knee ROM nor did we detect increased muscle co-activation (paper II).

Self-reported outcomes

Despite observing no deficits in muscle strength and functional performance 2 years post meniscectomy, patients self-reported worse knee specific pain and impaired function (ADL and Sport/Rec) along with more symptoms and reduced QOL on the KOOS questionnaire (Figure 11). The KOOS scores observed in paper I were similar to those previously reported in meniscectomized patients 4 years post meniscectomy (Ericsson et al., 2006). Furthermore, our patients reported more bodily pain and worse physical function on the generic SF-36 questionnaire (paper I). This indicate that factors other than muscle strength are responsible for the perceived functional limitations and suggest as such that training to improve strength alone may not be sufficient to improve self-reported function in patients at high risk of knee OA. The non-significant relationship observed between Sport/Rec and muscle strength variables at 2 years post meniscectomy (paper I) support this notion and indicate that the tests measure different constructs. Other likely candidates than maximal isolated leg muscle strength to influence self-reported Sport/Rec function include pain, mental health, general fitness (VO_2max) and physical activity level. Furthermore, self-reported knee function has been shown to be related to general subject characteristics like age, gender and BMI (Paradowski et al., 2005, Paradowski et al., 2006). A backward stepwise multiple regression analysis with these variables was conducted to explore other potential determinants of self-reported sport and recreational function (Sport/Rec) at 2 years post meniscectomy (paper I). Meniscectomy, poor mental health and higher BMI were found to be associated with worse KOOS Sport/Rec function (multiple regression coefficient $r^2=0.52$, $p<0.001$). Having had a meniscectomy was the strongest predictor ($r^2=0.35$) of worse Sport/Rec function score in the model. Other factors like fear of pain and re-injury or low self-efficacy could also affect self-reported function but these aspects were not evaluated.

At the follow-up 4 years post meniscectomy it seemed that patients self-reported less problems on the KOOS sub scales compared to 2 years post meniscectomy (Figure 11) and the absolute mean values were somewhat lower compared to what Ericsson et al. (Ericsson et al., 2006) observed 4 years post meniscectomy. Explanations for this seemingly improvement with time may include true improvement but may also be caused by loss to follow-up. Additional analysis comparing baseline KOOS data for patients participating in the full follow-up examination 4 years post meniscectomy (n=22) (i.e. physical tests and KOOS questionnaire) to drop-outs and patients only replying the questionnaire (n=9) showed that patients dropping out or not participating in the physical examination at follow-up self-reported significantly worse on all KOOS subscales at baseline ($p<0.01$). In contrast, no differences were observed between controls participating in the physical examination (n=25) and those dropping out or only replying the KOOS questionnaire (n=6) ($p=0.20-0.85$). This analysis support the notion that the apparent improvement in patients KOOS scores at follow-up is primarily attributed to loss-to-follow-up bias.

Methodological considerations

Subjects

Strict inclusion/exclusion criteria were used to include a homogeneous group of middle-aged patients with degenerative medial meniscus tears. Thus, the results of the present thesis cannot be generalized to all meniscectomized patients since the results may not apply to younger patients who have with traumatic tears.

Study groups (i.e. patients and controls) were not exactly matched on gender which could potentially have influenced the present results. Thus, all variables concerning strength and functional capacity were adjusted for age and sex in paper I and III.

Five patients had an injury to the contra-lateral knee. These patients were not excluded in paper I and III since our a priori hypothesis was a bilateral strength deficit between patients and controls. Furthermore, their results in the strength and functional tests remained within two standard deviations of the mean of the non-operated leg and additional sensitivity analysis introducing unilateral/bilateral injury as a fixed effect in the mixed model did not change interpretation of data. Due to the mechanistic focus of paper II patients self-reporting knee injuries to the contra-lateral knee were excluded.

Drop outs of patients and controls occurred from the baseline to the follow-up examination (i.e. 4 patients and 3 controls). However, physical characteristics (age, BMI and aerobic power) did not differ between patients (n=4) and controls (n=3) that dropped out compared to those who stayed in the study, except that drop out controls showed a higher hand grip strength than control subjects who stayed in the study. Furthermore, some patients (n=5) and controls (n=3) did not perform the physical tests but only replied the KOOS questionnaire. Patients only replying the questionnaire self-reported worse on all KOOS subscales compared to those patients who completed the physical tests. To take this into account, all statistics on changes from 2 to 4 years post meniscectomy in muscle strength variables and functional performance were adjusted for values at 2 years post meniscectomy (paper III).

Outcomes

In the present thesis several different methods were employed to capture different aspects of neuromuscular function including self perceived function.

Reliability of the selected outcome measures were not tested in the present thesis since groups were primarily compared cross-sectionally. Furthermore, when comparing between groups, reliability of tests is expected to affect both groups similarly. Most outcomes have previously been tested for reliability in similar patients. Isokinetic strength testing reliability has been tested in numerous studies on healthy participants (Lund et al., 2005, Sole et al., 2007, Impellizzeri et al., 2008), patients with knee osteoarthritis (Kean et al., 2010) and patients with ACL injuries (Brosky, Jr. et al., 1999). The reliability of the two functional performance tests used in the present thesis have previously been tested in patients similar to those in the present thesis (Bremander et al., 2007). Furthermore, the KOOS questionnaire has been tested for reliability and validity (Roos et al., 1998a, Roos et al., 1998b) and has been used in numerous studies investigating patients with different types of knee problems and degree of knee pain like meniscus injury, ACL injury and knee osteoarthritis.

In the present thesis a novel setup was used investigating the transition step between stair descent and level walking as this step involves the highest peak GRF forces and was thus considered the most demanding part of stair descent for the knee joint. The reliability of the stair descent protocol and hence kinematic, kinetic and EMG variables were not evaluated in the present thesis. Electro goniometers have previously shown moderate to good intra-tester reliability (ICC 0.75-0.88) for assessing static knee joint position (Piriyaprasarth et al., 2008) as well as during gait (Isacson et al., 1986). Stacoff et al. (Stacoff et al., 2005) has previously reported a low coefficient of variations during stair descent (5-8%) using similar methods as in the present thesis to define and evaluate ground reaction forces (except for the loading slope which had coefficients of variation of 15-16%). On the basis of these results and experience from a previous study from our laboratory (Larsen et al., 2008) only minor acceptable variation were expected. Using 3D motion analysis would have reduced variation, increased sensitivity and allowed for calculation of knee joint moments using inverse dynamics but this were not possible in the present thesis due to methodological restraints. EMG measurements are generally less reliable than other biomechanical methods showing moderate to good reliability (ICC 0.53-0.88 depending on the muscle examined) (Clark et al., 2007). This variability is probably attributed to the numerous factors that can influence the surface EMG signal (i.e. temperature, skin impedance, muscle architecture, electrode configuration, etc.) (Keenan et al., 2005). Nevertheless, the EMG recording method offers information about the degree of muscle activity that cannot be evaluated with other methods, but the results must always be interpreted with caution. In this thesis EMG was normalized to maximal EMG amplitude during a MVC. It has been suggested that normalization to maximal EMG amplitude is not appropriate in patients since maximal effort may not be reached in the trials used for normalization due to pain. However, in the present study there were no indications that pain was a limitation for maximal effort since patients performed equally well as controls at the baseline examination during maximal muscle strength testing. Furthermore, no or negligible pain was reported on a 100 mm VAS scale following strength testing.

Clinical implications

This thesis demonstrate that patients meniscectomized for degenerative meniscus tears experience pain, functional limitations and reduced quality of life compared to population-based controls. Despite reductions in self-reported outcomes no impairments in maximal muscle strength or rapid force capacity were observed between patients and population-based controls 2 years post meniscectomy indicating that other factors than muscle strength are responsible for the functional limitations perceived by the patients (paper I). Nevertheless, alterations in kinematics and neuromuscular activity patterns were observed between the operated and contra-lateral leg of patients which may contribute to the perceived reductions in self-reported outcomes (paper II). Furthermore, changes in neuromuscular activation may precede deficits in maximal muscle strength which seemed to emerge in knee extensor muscle strength between the operated and contra-lateral leg of patients from 2 to 4 years post meniscectomy. This could be a potential window of opportunity for interventions to retain strength and potentially slow the development or decrease the risk of knee OA in these patients.

The hypothesized impairments in neuromuscular function between patients and controls could not be verified in the current thesis. Thus, the importance of the relatively modest leg-to-leg changes in patients in terms of neuromuscular function and their role in knee OA development may be limited. The observed reductions in medial muscle activity in meniscectomized legs may reflect an initial strategy to decrease compression forces in the medial compartment of the knee joint. No changes were observed in knee joint loading with the methods used in the present study. More precise methods to assess knee joint kinetics and kinematics, like 3D motion analysis, may be needed to detect early changes in knee joint biomechanics in patients at high risk of knee OA. Furthermore, Slemenda et al. (Slemenda et al., 1998) has previously shown that the development of knee OA over a ~2½ year period in older people (~70 years at baseline) was associated with 18% lower knee extensor strength in women. On the other hand, a more recent study reported reductions in knee extensor strength of only 7 and 9% in men and women of similar age as in the present thesis self-reporting knee or hip OA at ~14 years follow-up (Hootman et al., 2004). The latter results indicate that early impairments in neuromuscular function prior to OA may be very subtle as also observed in the present thesis.

Conclusions

- Overall thigh muscle strength, rapid force capacity and functional performance was not impaired in the operated leg of patients 2 years post meniscectomy compared to the contra-lateral leg or compared with controls.

- Middle-aged meniscectomized patients self-report substantial pain and functional limitations compared to population-based controls 2 years after resection of a symptomatic degenerative medial meniscus tear.

- No differences were observed between meniscectomized patients and controls in kinematics, kinetics and neuromuscular activity during stair descent 2 years after resection of a symptomatic degenerative medial meniscus tear. Kinematic differences were observed between the operated leg and the contra-lateral leg of patients along with reduced medial compared with lateral neuromuscular activity in the operated leg.

- No differences in changes over time were observed in knee flexor MVC, rapid force capacity or functional performance between the operated and contra-lateral leg of patients or compared with controls. A difference in knee extensor MVC evolved between the operated and contra-lateral leg of patients from 2 to 4 years post meniscectomy.

Perspectives

The present thesis combined methods of clinical research with laboratory based methods to investigate patient reported outcomes and detailed aspects of neuromuscular function in patients at high risk of knee OA. The results of this thesis suggest that impaired muscle strength is not responsible for the perceived functional limitations and indicate that alterations in kinematics and neuromuscular activity may precede muscle strength deficits, which seem to evolve over time in patients at high risk of knee OA. Future longitudinal studies should be conducted to investigate the proposed time course of changes in neuromuscular function and their effect on knee joint loading.

Summary

Musculoskeletal diseases are the most common chronic disorders and a huge burden to society affecting more than half of the adult Danish population within any two-week period. Osteoarthritis (OA) is the most common musculoskeletal disease disabling around 10% of the population above 60 years of age. OA is a slowly developing degenerative disease causing local destruction of the involved joint and the surrounding structures. The knee joint is most frequently affected resulting in pain, functional disability and reduced quality of life. Reduced neuromuscular function is considered a risk factor for knee OA. Meniscectomized patients constitute a sub-group at high risk of developing knee OA, with approximately half the patients showing radiographic signs of knee OA 10-15 years after meniscectomy. Meniscus tears referred to as symptomatic degenerative tears have been suggested to be associated with incipient OA and/or represent early stage OA in the middle-aged population. In this thesis patients meniscectomized for symptomatic degenerative tears were used as a model to study neuromuscular function prior to knee OA.

In the first study muscle strength, functional performance and patient perceived pain and function were examined in 31 patients 2 years after surgery for a degenerative meniscus tear and 31 population-based controls. Despite patients self-reporting pain and functional limitations no differences were observed in muscle strength and functional performance.

In the second study thigh neuromuscular activity and selected biomechanical variables were investigating in 22 patients and 26 controls during the transition step between stair descent and level walking. No differences were observed between patients and controls. However, modulations in kinematics and neuromuscular activity represented by a shorter stance phase and reduced overall medial vs. lateral thigh muscle activity in the meniscectomized leg compared with the contra-lateral leg in patients was observed.

The third study investigated the hypothesis that changes in muscle strength and functional performance would differ between patients and controls over 2 years time. Twenty-two patients and 25 controls participated in this follow-up study conducted 4 years post meniscectomy. Overall changes from 2 to 4 years post meniscectomy did not differ in maximal muscle strength and functional performance between patients and controls. However, post-hoc analysis revealed a difference in change in knee extensor MVC resulting in a 6% difference between the operated and contra-lateral leg of patients at follow-up 4 years post meniscectomy.

The results of this thesis suggest that impaired muscle strength is not responsible for the perceived functional limitations and indicate that alterations in kinematics and neuromuscular activity may precede muscle strength deficits which seem to evolve over time in patients at high risk of knee OA. The current findings may represent the initial stages in the possible chain of events leading to knee OA in meniscectomized patients.

Dansk resumé

Sygdomme i bevægeapparatet er de hyppigst forekommende kroniske lidelser, og de er en stor byrde for samfundet, idet disse, indenfor en hvilken som helst to ugers periode, påvirker mere end halvdelen af den voksne befolkning i Danmark. Artrose (slidgigt) er den hyppigste af disse sygdomme og invaliderer ca. 10 % af befolkningen over 60 år. Artrose ses oftest i knæleddet og er en langsomudviklende degenerativ sygdom, der forårsager ødelæggelse af det involverede led og de omkringliggende strukturer hvilket resulterer i smerte, invaliditet og nedsat livskvalitet. Nedsat neuromuskulær funktion anses som en risikofaktor for knæartrose. Meniskopererede patienter udgør en sub-gruppe med høj risiko for knæartrose, idet halvdelen af disse har radiografiske tegn på knæartrose 10-15 år efter operation. Degenerative skader på menisken anses for at være et tegn på artrose eller repræsentere første stadie af sygdommen i den midaldrende del af befolkningen. I denne afhandling anvendes patienter, der har fået foretaget meniskoperation for en degenerativ meniskskade, som en model til at undersøge neuromuskulær funktion før udvikling af knæartrose.

I første studie blev muskelstyrke, objektivt målt funktion samt patientrapporteret smerte og funktion undersøgt hos 31 patienter 2 år efter resektion af en degenerativ meniskskade samt hos 31 kontrolpersoner. På trods af at patienter selvrapporterede mere smerte og nedsat funktion, blev der ikke observeret forskelle i muskelstyrke og objektivt målt funktion.

I andet studie blev neuromuskulær aktivitet i låret samt udvalgte biomekaniske variabler undersøgt under udførslen af overgangsskridtet imellem gang nedad trappe og almindelig gang hos 22 patienter og 26 kontroller. Ingen forskelle blev registreret imellem patienter og kontroller. På trods af dette blev der observeret kinematiske ændringer samt ændringer i neuromuskulær aktivitet manifesteret ved en reduceret standfase samt reduceret medial vs. lateral muskelaktivitet i patienternes opererede ben i forhold til det kontra-laterale ben.

Tredje studie undersøgte om der var forskelle i ændringer i muskelstyrke og objektiv målt funktion imellem patienter og kontroller fra 2 til 4 år efter meniskoperation. Toogtyve patienter og 25 kontrolpersoner deltog i opfølgningsstudiet 4 år efter operation. Generelt var der ingen forskelle i ændringer imellem patienter og kontrolpersoner i maksimal muskelstyrke og objektivt målt funktion. Sekundær analyse viste en forskel i ændring i maksimal styrke i knæekstensorerne, hvilket resulterede i en forskel på 6 % imellem patienternes opererede og kontra-laterale ben ved opfølgningen 4 år efter operation.

Resultaterne fra denne afhandling antyder, at forringet muskelstyrke ikke er ansvarlig for patienternes oplevede funktionsnedsættelse. Desuden indikerer de, at kinematiske ændringer og ændringer i neuromuskulær aktivitet muligvis går forud for den forringelse i muskelstyrke, der ser ud til at opstå over tid hos patienter med høj risiko for udvikling af artrose. Disse fund repræsenterer potentielt den initielle fase i en række af hændelser, der fører til knæartrose hos meniskopererede patienter.

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Paper I

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ORIGINAL ARTICLE

Thigh Muscle Strength, Functional Capacity, and Self-Reported Function in Patients at High Risk of Knee Osteoarthritis Compared With Controls

JONAS BLOCH THORLUND, PER AAGAARD, AND EWA M. ROOS

Objective. **Reduced muscle strength is suggested as a risk factor for knee osteoarthritis (OA). Meniscectomy patients have an increased risk of developing knee OA. The aim of this study was to identify reductions in different aspects of muscle strength as well as objectively measured and self-reported lower extremity function in middle-aged patients who had undergone a meniscectomy compared with controls.**

Methods. **Thirty-one patients who had undergone surgery in 2006 and 2007 (mean ± SD age 46 ± 6 years, mean ± SD body mass index [BMI] 26 ± 4 kg/m^2, and mean ± SD postsurgery 21 ± 6 months) and 31 population-based controls (mean ± SD age 46 ± 6 years and mean ± SD BMI 26 ± 4 kg/m^2) were examined for maximal muscle strength and rapid force capacity, distance achieved during the one-leg hop test, and the maximum number of knee bends performed in 30 seconds. The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to determine self-reported outcomes.**

Results. **No differences were detected in any muscle strength variables between the operated and nonoperated leg (mean ± SD quadriceps maximum voluntary contraction of 2.80 ± 0.10 for the operated leg and 2.88 ± 0.10 for the nonoperated leg), between patients and controls (mean ± SD torque of 2.70 ± 0.09 Nm × kg^{-1} for the controls; $P = 0.26$ for main effect leg), or in objectively measured function ($P \geq 0.27$). Patients reported 10–26 points worse KOOS scores in all 5 subscales ($P < 0.001$).**

Conclusion. **Thigh muscle strength is not impaired in middle-aged adults 2 years after resection of a degenerative tear. Our findings indicate that factors other than muscle strength are responsible for the perceived functional limitations and suggest that training to improve strength alone may not be sufficient to improve self-reported function in patients at high risk of knee OA.**

INTRODUCTION

Reduced muscle strength is suggested as a risk factor for knee osteoarthritis (OA) (1–4). Meniscectomy patients constitute one subgroup at high risk of developing knee OA (5,6), with approximately one-half of the patients showing radiographic signs of knee OA 10–15 years after undergoing a meniscectomy (6–8). Meniscus tears, referred to as symptomatic degenerative tears, have been suggested to be associated with incipient OA and/or represent early-stage OA in the middle-aged population (9,10). Therefore, patients undergoing surgery for symptomatic degenerative tears constitute a model to study the state prior to knee OA.

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In meniscectomy patients, conflicting results have been reported on the rehabilitation of muscle strength and functional performance in the operated leg compared with the nonoperated leg (11–17). In one study, where a control group was included, a reduction in bilateral quadriceps maximal voluntary contraction (MVC) and voluntary activation was observed in meniscectomy patients (18), but no differences were seen between the operated and nonoperated leg. This finding suggests bilateral muscular deficits and emphasizes the need for a control group if the magnitude and nature of lower extremity muscle strength deficiencies in these patients are to be identified and examined.

Testing maximal isometric muscle strength might not adequately describe all aspects of lower extremity muscle function and changes in functional performance compared with healthy controls. For instance, reduced levels of eccentric thigh muscle strength might reduce the ability to absorb impacts and thereby increase knee joint loading (19). Furthermore, impaired capacity for rapid force exertion (i.e., a right shift in the torque time curve indicating a reduced rate of force development [RFD]) is thought to be important for functional performance (20). Reduced rapid force capacity would decrease the percentage of force produced in the early phase of muscle contraction and thereby reduce the ability to react on sudden perturbations, potentially representing a functional deficiency in postural control and other types of reactive motor tasks. Understanding in detail these muscle strength deficiencies and their relationship to self-reported function in patients at high risk of knee OA would be important in clinical decision making and in developing future knee OA prevention regimens.

The aim of the present study was to identify reductions in various aspects of muscle function for the knee extensor and flexor muscles (i.e., maximal concentric, eccentric, and isometric muscle strength, as well as rapid force capacity) together with deficiencies in objectively measured and self-reported physical function in middle-aged meniscectomy patients compared with population-based controls. It was hypothesized that meniscectomy patients would show a bilateral deficiency in muscle strength and objectively measured function compared with controls.

PATIENTS AND METHODS

Patients. Patients ages 35–55 years at the time of surgery, who had undergone surgery in 2006 and 2007 for a medial meniscal tear in the posterior half of the meniscus, were identified through the surgical code system from 2 different hospitals. The age criteria were set to include a majority of patients with degenerative meniscal tears but without knee OA. Patients were excluded if they were misclassified by the surgical code system, or if they had a previous knee ligament injury, severe cartilage changes defined as deep clefts or visible bone at the time of the meniscectomy, or self-reported comorbidities limiting participation in the study. A modified version of the Self-Administered Comorbidity Questionnaire, developed by Sangha et al (21), was used to identify comorbidities. After their meniscectomy, patients were given a leaflet with standard rehabilitation exercises, which they were encouraged to perform at home. Information on compliance with the exercise recommendation was not collected.

Age- and sex-matched controls were identified through the Danish Civil Registration System. An invitation was sent to a total of 600 people living in the same geographic area as the meniscectomy patients. Those who accepted the invitation received the modified version of the Self-Administered Comorbidity Questionnaire (21). Subjects were excluded if they had had a previous knee ligament injury, knee surgery, or self-reported comorbidities limiting participation in the study. Eligible controls were stratified into 4 groups: men ages 35–45 years, men ages 46–55 years, women ages 35–45 years, and women ages 46–55 years. For every patient who was included in the study, a control was randomly selected from the appropriate age group by use of a random number generator. All testing was conducted in the period from August to November 2008.

Test procedures. Testing was done on 2 separate occasions. On the first occasion the informed consent form was signed and the subjects answered the Short Form 36 (SF-36) health survey and the Knee Injury and Osteoarthritis Outcome Score (KOOS), both self-administered questionnaires. Then body height and weight were measured, and the patient's fat free mass was estimated by a conventional bioimpedance leg-to-leg method (TANITA TBF-305, Tanita). The subjects were then tested for the maximum number of knee bends they could perform within 30 seconds and for the distance they could cover in the one-leg hop test (22). All muscle strength tests were carried out in an isokinetic dynamometer (Kinetic Communicator 500H, Chattecx) on the second occasion ~7 days later. Also on the second occasion, subjects were asked to report the amount of vigorous and moderate physical activity in which they had engaged during work and leisure time over the previous 7 days. Subjects then performed a warm-up activity consisting of a submaximal bicycle exercise test, during which maximal oxygen consumption ($V\mathrm{O}_{2\mathrm{max}}$) was estimated using Åstrands nomogram (23). Finally, the muscle strength tests were conducted. The order of test leg was randomized for both groups on both testing occasions (i.e., operated/nonoperated in the patients and left/right in the controls). The study was approved by the ethics committee of the Region of Southern Denmark.

Outcome measures. *Muscle strength testing.* Placement of subjects in the isokinetic dynamometer was conducted as previously described (24,25). The dynamometer force and position signals were recorded by a personal computer at a 1,000 Hz sampling rate during isometric tests and a 100 Hz rate during dynamic tests, and was filtered by a fourth-order zero-lag Butterworth low-pass filter at 15 Hz cutoff frequency. To correct for the effect of gravity on the measured joint torques, the passive mass of the lower leg was measured in the dynamometer at a knee joint angle of 45° (26). In addition to the submaximal bicycle warm-up, subjects performed a further warm-up and preconditioning exercise in the dynamometer, which consisted of 4 concentric and 3 eccentric contractions, gradually increasing force. Subsequently, maximal concentric, eccentric, and isometric muscle strength were measured unilaterally in the knee extensors and knee flexors in both legs of all participants. Knee joint angular velocity during dynamic testing was set to 30°/second with a knee joint range of motion from 90° to 20° (0° = full knee extension). Successive trials at each contraction mode were conducted until the subject was unable to further increase peak torque (4–6 trials were typically conducted).

Isometric MVC was measured at a 70° knee joint angle (best of 3 trials) during knee extension and flexion, respectively. The average slope (△ torque/△ time) at time points 0–30, 50, 100, and 200 msec of the torque time curve was calculated to evaluate the capacity for rapid force production. These time intervals have previously been used to assess RFD in the initial phase of muscle contraction in healthy patients (25,27) and in surgical patients (20). The onset of contraction was defined as the instant where force increased by 2% of peak torque above the resting baseline level. Visual feedback of the dynamometer torque output was provided to the subjects on a computer screen after

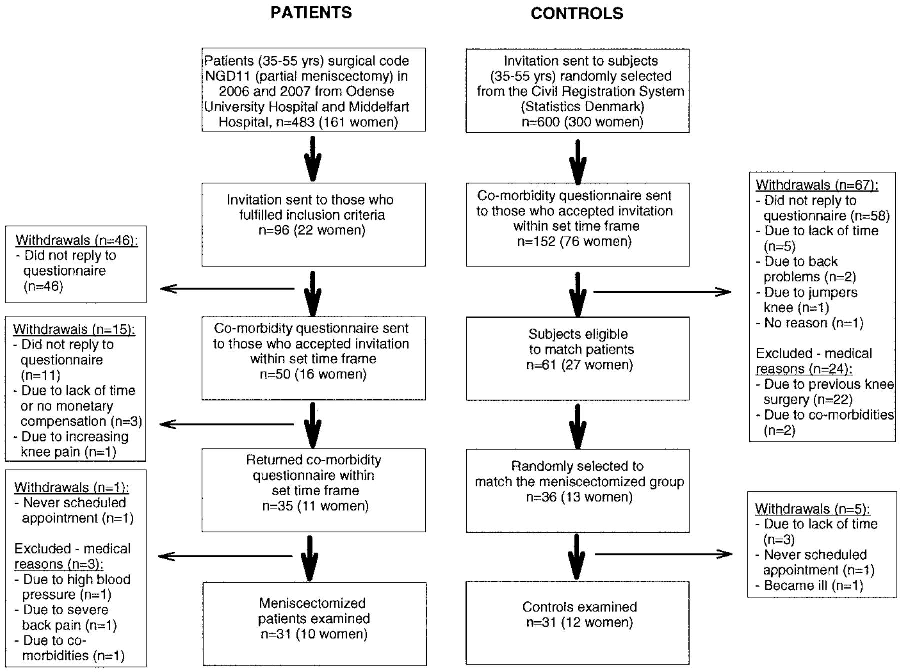

Figure 1. Flow chart of the recruitment process for the meniscectomy patients and controls.

each trial (28). The reliability and validity of the KinCom dynamometer have previously been verified in detail (29).

Self-reported outcomes. The KOOS was used to assess function during activities of daily living (ADL) and during sport and recreation function (Sport/Rec). The KOOS also assesses pain, other symptoms, and knee-related quality of life (30). A normalized score is calculated for each subscale (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS score has been validated for meniscectomy patients and has shown high test–retest reproducibility (30,31).

The SF-36 was used to assess general physical function (32). The SF-36 consists of 8 subscales: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The SF-36 is self-explanatory, takes ~10 minutes to complete, and is scored from 0–100 (0 = extreme problems and 100 = no problems). The Acute Danish version of the SF-36 was used (33,34).

Physical activity level was reported as the amount (in hours and minutes) of vigorous and moderate physical activity undertaken during the previous 7 days and reported separately for work and leisure time. Each period of physical activity had to last for at least 10 minutes at a time. Vigorous physical activity was defined as activity that makes one breathe harder than normal, and moderate physical activity was defined as activity that makes one breathe somewhat harder than normal.

Functional capacity tests. The one-leg hop test (35) has been shown to be valid and reliable in meniscectomy patients (22). The subject stands on one foot with the hands on the back and is asked to jump as far as possible and land steadily on the same foot. The subject has to be able to land and stand long enough for the examiner to measure the length of the jump. At least 3 trials with 60-second rest periods between each attempt (or until the subject made no further progress) were conducted, and the longest jump was recorded.

The maximum number of knee bends performed in 30 seconds (16) has also been shown to be a valid and reliable test in meniscectomy patients (22). The subject's long axis of the foot was aligned with a straight line and the toes placed on a perpendicular line; light fingertip support was provided to the subject by the examiner to aid balance. The subject was asked to flex the knee while standing on one leg, without bending forward at the hip, until the line along the toes was no longer visible to the subject (~30° knee flexion). The maximum number of knee bends performed in 30 seconds was recorded.

Statistical analysis. Becker et al have previously reported a difference of ~20% in quadriceps MVC between meniscectomy patients and controls (18). To detect a similar difference in quadriceps MVC (80% power with a significance level of 0.05), our sample size calculation indicated a need for 25 individuals in each group. Student's unpaired *t*-test and the Mann-Whitney test were used to compare subject characteristics between patients and controls, as appropriate. To evaluate the differences in strength variables and functional performance of the patient and control legs, a mixed linear model was used with "subject" as random effect and "leg" (i.e., operated, nonoperated, and control legs), "sex," and "age" as fixed effects (i.e., applying age as a continuous covariate). Differences among legs in the torque time curve pattern (and therefore RFD) were also assessed by using a mixed linear model with the combination of "subject" and "side" (i.e., repeated nested measurements on each leg of the subjects) as random effects and "leg" (i.e., operated, nonoperated,

Table 1. Characteristics of subjects*

	Patients (n = 31)	Controls (n = 31)
Subjects, no. male/female	21/10	19/12
Time since surgery, months	20.6 ± 6.1	N/A
Age, years	46.0 ± 5.5	45.9 ± 5.8
Height, cm	174.5 ± 6.9	175.0 ± 9.1
Weight, kg	77.7 ± 14.0	78.5 ± 16.3
Body mass index, kg/m^2	25.5 ± 3.8	25.5 ± 4.3
Fat free mass, kg	57.8 ± 9.4	58.5 ± 12.0
VO_{2max}, ml $O_2 \times kg^{-1}$	35.8 ± 8.9†	37.0 ± 11.1
Hand grip strength, kg	39.1 ± 9.1	38.1 ± 8.8
Vigorous and moderate physical activity level, hours/week‡		
Work	2.3 (0, 16)†	0.0 (0, 1)§
Leisure	0.9 (0, 2.5)†	1.3 (0, 3)
Self-reported comorbidities¶		
1–2 musculoskeletal, no.	13	11
1–2 general, no.	6	10

* Values are the mean ± SD unless otherwise indicated. N/A = not applicable; VO_{2max} = maximal VO_2.
† N = 30.
‡ Distribution of physical activity was skewed and is shown as the median (25th, 75th percentiles).
§ Significantly different than patients ($P \leq 0.05$ by Mann-Whitney test).
¶ For which subjects were either treated and/or no limitation imposed for study participation. Musculoskeletal comorbidities reported other than knee: joint problems and back pain. General comorbidities reported: high blood pressure, diabetes mellitus, ulcer, heart problems, and depression.

and control legs), "sex," "age," and "time point" (i.e., 0–30, 50, 100, and 200 msec) as fixed effects. Age and sex were introduced in the models to adjust for potential confounding, as anticipated in classic epidemiology. The Mann-Whitney test was used to compare self-reported outcomes (i.e., KOOS and SF-36 scores) in patients and controls. Correlation analyses were performed by calculation of Spearman's rho to assess the relationship between Sport/Rec and concentric, eccentric, and isometric peak torque. Stata software, version 10.1 (StataCorp) was used for all statistical analyses, with the prespecified level of significance equal to 0.05.

RESULTS

A detailed overview of the recruitment flow is shown in Figure 1. Thirty-one patients (10 women) and 31 controls (12 women) were ultimately examined. Due to a slow recruitment process of patients in the beginning of the study, the first 7 controls were included before patients were included, which is the reason for the discrepancy between the number of women, 10 and 12, respectively, in the patient and control groups. Therefore, the study is matched on a group level instead of on a case level.

Characteristics of patients and controls are shown in Table 1. No differences were observed between patients and controls except for physical activity at work, where patients were more active than controls. At the first test session, 5 patients reported knee injuries (which had not been reported previously) in the contralateral knee, 3 patients underwent a meniscectomy, 1 patient had a deficient anterior cruciate ligament (ACL), and 1 patient had an ACL reconstruction and meniscectomy. These patients were not excluded since our a priori hypothesis was a bilateral strength deficit between patients and controls. Furthermore, their results in the strength and functional tests were within 2 SDs of the mean of the nonoperated leg. All other patients had a healthy control leg.

Thigh muscle strength and objectively measured functional capacity. Overall, no differences were observed between the operated and nonoperated legs of the patients or when compared with controls in any of the strength variables (Table 2). No differences were observed in rapid force capacity (i.e., no right shift in the torque time curve

Table 2. Isokinetic muscle strength and functional performance tests*

	Patients			
	Operated leg (n = 31)	Nonoperated leg (n = 31)	Controls (n = 31; 62 legs)	*P*
Isokinetic muscle strength†				
Knee extension, Nm × kg^{-1}				
Concentric peak torque	2.66 ± 0.08	2.73 ± 0.08	2.55 ± 0.07	0.20
Eccentric peak torque	3.37 ± 0.12	3.48 ± 0.12	3.27 ± 0.11	0.29
Isometric MVC	2.80 ± 0.10	2.88 ± 0.10	2.70 ± 0.09	0.26
Knee flexion, Nm × kg^{-1}				
Concentric peak torque	1.37 ± 0.05	1.39 ± 0.05	1.39 ± 0.04	0.84
Eccentric peak torque	1.76 ± 0.07	1.79 ± 0.06	1.87 ± 0.06	0.46
Isometric MVC	1.20 ± 0.05	1.26 ± 0.05	1.20 ± 0.04	0.23
Functional performance				
Knee bends/30 seconds, no.	25.8 ± 1.8	26.1 ± 1.8	28.6 ± 1.8	0.45
One-leg hop, cm	82.4 ± 4.5	84.5 ± 4.5	91.1 ± 4.3	0.27

* Values are the mean ± SE, adjusted for age and sex. Mixed linear model. *P* indicates main effect of "leg." MVC = maximum voluntary contraction.
† Isokinetic test patients, n = 29. One patient failed to meet for the second test, and 1 patient did not complete the test due to severe pain after the warm-up procedure.

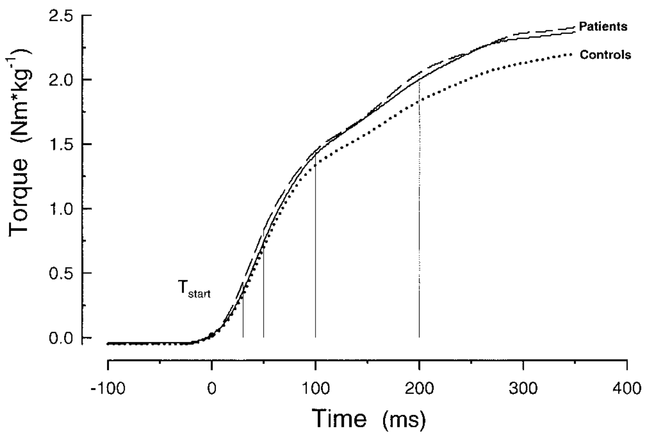

Figure 2. Mean torque time curve during knee extension for the operated leg (solid line), nonoperated leg (broken line), and control legs (dotted line). No difference in rapid force capacity using the time points 0–30, 50, 100, and 200 msec among any of the legs (mixed linear model).

and therefore no reduction in RFD) during maximal isometric knee extension ($P = 0.18$) (Figure 2) and knee flexion ($P = 0.71$) (data not shown). Furthermore, no significant differences were observed in the one-leg hop test or the maximum number of knee bends in 30 seconds test (Table 2).

Self-reported function and other outcomes. Patients reported worse knee function than controls in the KOOS subscales for ADL ($P \leq 0.001$) and for Sport/Rec ($P \leq 0.001$), as well as worse general physical function scores for the SF-36 subscale ($P \leq 0.001$). Additionally, patients reported more knee pain, bodily pain, other knee symptoms, and worse knee-related quality of life scores than controls (Figures 3 and 4).

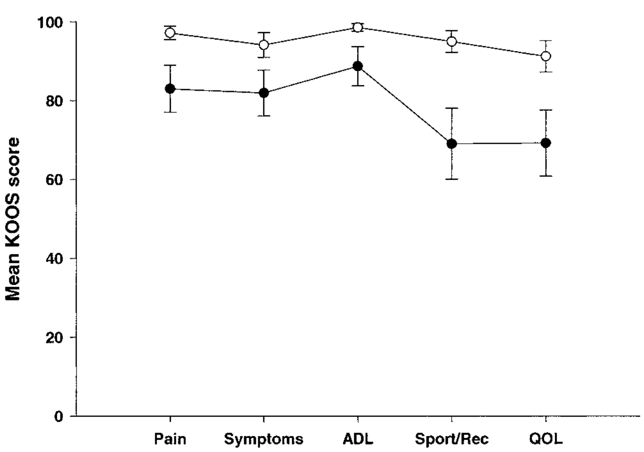

Figure 3. Knee Injury and Osteoarthritis Outcome Score (KOOS) results for the meniscectomy group (solid circles) and the control group (open circles). Scores are means with 95% confidence intervals presented as an outcome profile of the 5 dimensions of the KOOS scale, where a score of 100 represents no knee problems and a score of 0 represents extreme problems. There was a significant difference in all subscales ($P \leq 0.001$) between meniscectomy patients and controls (Mann-Whitney test). ADL = activities of daily living; Sport/Rec = sports and recreation; QOL = quality of life.

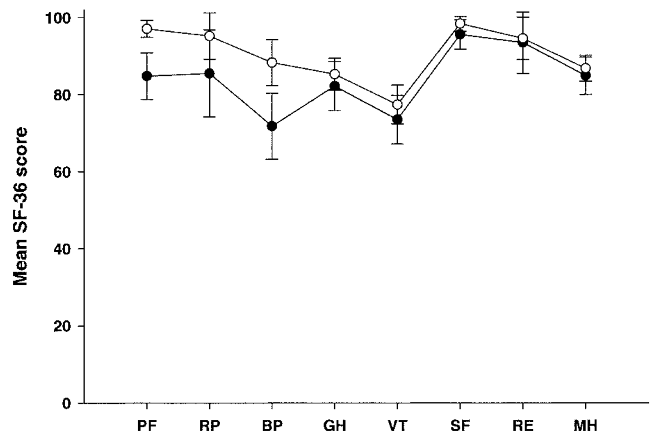

Figure 4. Short Form 36 (SF-36) health survey results for the meniscectomy group (solid circles) and the control group (open circles). Scores are means with 95% confidence intervals presented as an outcome profile, where a score of 100 represents no problems and a score of 0 represents extreme problems. There was a significant difference (Mann-Whitney test) between meniscectomy patients and controls in PF ($P \leq 0.001$) and BP ($P \leq 0.01$). PF = physical function; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social function; RE = role emotional; MH = mental health.

Relationships between self-reported function and objectively measured function and maximal muscle strength. Weak and nonsignificant correlations were observed between Sport/Rec and the various muscle strength variables, i.e., concentric and eccentric peak torque and isometric MVC ($r_s = 0.07–0.23$, $P \geq 0.22$).

DISCUSSION

To our knowledge, the present study is the first to examine detailed aspects of muscle strength together with objectively measured and self-reported functional capacity in meniscectomy patients compared with age- and sex-matched controls. Despite that, patients in accordance with previous studies reported impaired function, elevated pain, and more symptoms than controls (17,36,37). The hypothesized bilateral reductions in various muscle strength variables and functional tests between patients and controls were not observed. Likewise, no differences were observed between the operated and nonoperated leg in the patients, even though this finding could be masked by the patients with injuries to the contralateral knee.

Previous knee injury and reduced muscle strength are considered risk factors for knee OA (1,2,38). This study investigated different aspects of muscle strength and functional capacity in meniscectomy patients who were considered to represent a "pre-OA" state (10,18). Some previous studies report quadriceps strength deficiencies (11,13), whereas others observe no difference in muscle function (12,14,15) when comparing the operated with the nonoperated leg in meniscectomy patients. In 2 recent studies on strength deficiencies 4 years after meniscectomy in patients similar to those in the present study, impaired knee extensor strength and functional capacity were observed in the operated versus the nonoperated leg (17) and bilaterally compared with controls (18). The present study was conducted to combine the strength of these 2 studies by elucidating detailed aspects of muscle strength and functional performance impairments in meniscectomy patients compared with age- and sex-matched controls, and relating these aspects to self-reported knee function. Unexpectedly, however, the initial hypothesis of bilateral strength deficiencies between patients and controls could not be verified. Furthermore, no differences were detected between the operated and nonoperated legs of the meniscectomy patients in maximal muscle strength and functional capacity tests (Table 2 and Figure 2).

The discrepancies between the muscle strength data obtained in the present study and previous studies (17,18) might be due to differences in patient selection, selection of controls, and/or methodologic differences. In fact, patient recruitment per se could be suspected to be a major reason for the divergent results on muscle strength reported in meniscectomy patients. The recruitment process is often sparsely reported in previous studies. Patient recruitment from a clinical setting or advertising for patients may introduce selection bias toward patients with more symptoms. In the present study, great care was taken during the recruitment process to ensure that patients were representative of a population who had undergone a meniscectomy for a degenerative tear. Furthermore, the meniscectomy patients in the present study were very similar to controls except for the self-reported knee problems (Table 1 and Figure 3). In the study by Becker et al (18), none of the patients participated in sports activities and no information on participation in sports was given for the controls. Therefore, the reported difference between the patients and controls (18) might be influenced by a higher level of physical activity in the control group. In the current study, patients self-reported more moderate and vigorous physical activity at work than controls, whereas physical activity during leisure time was equal between the patient and control groups (Table 1). However, general muscle strength (grip strength) and general fitness ($\dot{V}O_{2max}$) were equal in patients and controls supporting similar physical activity levels (Table 1). In the present study, controls were not excluded if they had minor self-reported comorbidities that were similar to those of the patients, since this was to be expected in a population of middle-aged individuals. No information was given on comorbid conditions in the study by Becker et al (18); therefore, it is not possible to know if different levels of comorbidities between the studies could help explain the inconsistent results.

In the current study, patients were examined ~21 months after their meniscectomy, whereas in the studies by Becker et al (18) and Ericsson et al (17), patients were examined ~48 months postmeniscectomy. Therefore, it is possible that the patients in our study showed no reduction in muscle strength, since the potential development of knee OA may not have progressed as dramatically due to the shorter postsurgery time interval. However, the ages of the participants in the present study and the 2 previous studies are similar, with a mean age range of 42.8–46.0 years (17,18).

Changed muscle activation patterns and increased agonist–antagonist coactivation have been observed in knee OA patients compared with healthy age-matched controls (39–42). Hence, impaired neuromuscular function might precede knee OA and also precede muscle weakness. It seems from the present results that when patients performed isolated unilateral single-joint motor tasks in an isokinetic dynamometer, a test with very few degrees of freedom, no difference in performance was observed compared with controls. However, in functional tests that rely more on sensory input and postural (sensory motor) control, there was a borderline clinically relevant difference of 10% between patients and controls. The study was, however, not statistically powered to detect this difference, since sample size estimation was done on quadriceps MVC. Consequently, future studies should examine whether meniscectomy patients have altered neuromuscular activity when performing functional tasks/daily activities or whether sensory input is impaired. Another implication of these findings is that it might be useful if the training of symptomatic patients at risk of OA included training to increase neuromuscular control instead of only muscle strengthening.

A weak and nonsignificant relationship was observed between Sport/Rec and muscle strength variables, indicating the tests were measuring different constructs. Factors other than maximal isolated leg muscle strength could potentially also affect self-reported knee function. Factors like pain, mental health, general fitness ($\dot{V}O_{2max}$), and physical activity level are likely candidates to influence self-reported Sport/Rec function. Furthermore, self-reported knee function has been shown to be related to general subject characteristics like age, sex, and body mass index (BMI) (43,44). A backward stepwise multiple regression analysis with these variables was conducted to explore other potential determinants of self-reported Sport/Rec function. Meniscectomy, poor mental health, and a higher BMI were found to be associated with worse KOOS Sport/Rec function (multiple regression coefficient $r^2 = 0.52$, $P < 0.001$). Having had a meniscectomy was the strongest predictor ($r^2 = 0.35$) of a worse Sport/Rec function score in the model. Other factors like fear of pain and re-injury or self-efficacy could also affect self-reported function, but we have not evaluated these aspects.

There are some limitations to the present study. The results cannot be generalized to all meniscectomy patients since we followed strict inclusion/exclusion criteria to include a majority of patients with degenerative meniscal tears. Therefore, the results may only apply to middle-aged patients with degenerative tears and not to younger patients who have experienced traumatic tears. Furthermore, only approximately one-third of the patients who received an invitation participated in the study. We have no information on patients that did not participate in the study and direction of any bias due to this can only be speculative. However, the patients self-reported the same amount of pain, symptoms, and functional limitations as previously seen in other studies with similar patients (17,37). Controls from the same geographic region as the patients were recruited through the Danish Civil Registration System. Nevertheless, one cannot be sure that the controls are representative of the general population from which they were recruited, even though care was taken during the recruitment process to exclude only controls with knee problems related to the research question and to include controls with minor comorbidities common in the general population to this age group.

Study groups (i.e., patients and controls) were not exactly matched on sex (i.e., 10 and 12 women in the patient and control groups, respectively), which could potentially have influenced the results. However, all variables concerning strength and functional capacity had been adjusted for age and sex. Five patients had an injury to the contralateral knee. These patients were not excluded since our a priori hypothesis was a bilateral strength deficit between patients and controls. Furthermore, their results in the strength and functional tests were within 2 SDs of the mean of the nonoperated leg. However, it cannot be ruled out that these patients could mask differences between the operated and nonoperated leg. Excluding these 5 patients from the analysis resulted in a difference range of 6–8% in isometric quadriceps and hamstrings strength between the patients' operated and nonoperated legs, respectively. Differences less than 10% are often not considered clinically relevant (see supplementary Table 1, available in the online version of this article at http://www3.interscience.wiley.com/journal/77005015/home).

In conclusion, thigh muscle strength is not impaired in middle-aged adults 2 years after resection of a degenerative meniscal tear. Our findings indicate that factors other than muscle strength are responsible for the perceived functional limitations and suggest that training to improve strength alone may not be sufficient to improve self-reported function in patients at high risk of knee OA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Thorlund had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Thorlund, Roos.

Acquisition of data. Thorlund.

Analysis and interpretation of data. Thorlund, Aagaard, Roos.

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Paper II

Neuromuscular Function during Stair Descent in Meniscectomized Patients and Controls

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ABSTRACT

THORLUND, J. B., E. M. ROOS, and P. AAGAARD. Neuromuscular Function during Stair Descent in Meniscectomized Patients and Controls. *Med. Sci. Sports Exerc.*, Vol. 43, No. 7, pp. 1272–1279, 2011. **Purpose**: The aim of this study was to identify differences in knee range of motion (ROM), movement speed, ground reaction forces (GRF) profile, neuromuscular activity, and muscle coactivation during the transition between stair descent and level walking in meniscectomized patients at high risk of knee osteoarthritis (OA) compared with the nonoperated leg and with healthy controls. **Methods**: A total of 22 meniscectomized patients (15 men and 7 women (mean ± SD), 45.4 ± 5.1 yr, 174.3 ± 7.1 cm, 77.3 ± 15.4 kg) and 26 healthy controls (16 men and 10 women, 45.6 ± 6.1 yr, 174.9 ± 8.1 cm, 78.6 ± 16.8 kg) were tested using synchronous force plate, goniometer, and EMG recording (vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), semitendinosus (ST)) during the transition step between stair descent and level walking. Pain was assessed using the Knee Injury and Osteoarthritis Outcome Score. **Results**: Patients reported more pain than controls ($P \leq 0.001$), but no differences were observed between patients and controls in any variables including knee ROM during stance (operated leg = 42.9°, nonoperated leg = 44.3°, controls = 43.4°, respectively, $P = 0.42$). A shorter stance phase (T_{stance}; 657 vs 679 ms) was observed for the meniscectomized leg versus the nonoperated leg in patients along with reduced overall medial versus lateral thigh muscle activity in the meniscectomized leg during the weight acceptance phase ($P \leq 0.05$) and at peak GRF ($P \leq 0.01$). **Conclusions**: Patients and controls did not differ in any of the examined variables. However, kinematic differences were observed in the meniscectomized leg compared with the nonoperated leg along with attenuated medial leg muscle activity in the meniscectomized leg. The present findings support the hypothesis that meniscectomized individuals demonstrate early modulations in kinematics and neuromuscular activity that may represent an initial phase in the development of knee OA. **Key Words:** KNEE JOINT, OSTEOARTHRITIS, MENISCECTOMY, BIOMECHANICS, EMG

Patients with knee osteoarthritis (OA) self-report pain and functional limitations (20,34). The reductions in physical function have been associated with reduced muscle strength in the lower extremities (20,34,39), together with altered neuromuscular control thought to affect knee joint kinematics and kinetics during level gait and stair ascent/descent (11,14,16,17,32). However, it is not known whether these changes precede or follow because of knee OA.

Meniscectomized patients are at high risk of developing knee OA and thus constitute a good model to study OA onset (7,8). In a recent study on middle-aged meniscectomized patients, no reductions were reported in any muscle strength variables despite patients self-reporting more pain and reduced physical function compared with healthy controls ~2 yr after meniscectomy (37). However, a clinically relevant difference of ~10% was observed between meniscectomized patients and controls in clinical tests, indicating impairments in functional tasks with multiple degrees of freedom (37). Reduced functional capacity may reflect a movement strategy to minimize pain and to protect the knee joint by reducing joint range of motion (ROM) and movement speed and may, as such, be accompanied by altered patterns of neuromuscular activity. Changes in neuromuscular activity might involve increased muscle coactivation and altered medial versus lateral muscle activity, which have been previously reported in knee OA patients (11,14–17,19,32).

Changes in the neuromuscular activity pattern of prime mover thigh muscles in OA patients could potentially affect the focal concentration of bone-on-bone contact forces in the knee joint during locomotion. Further, long-term alterations in neuromuscular activity profile may precede future muscle strength deficits and either contribute *per se* to the development of OA or, alternatively, reflect an adoptive countermeasure strategy that is insufficient to prevent OA development. Stair descent constitutes a useful model to investigate such potential changes in neuromuscular control and loading, representing a demanding complex daily locomotor task with multiple degrees of freedom.

Several longitudinal training studies have demonstrated that resistance training and neuromuscular training can induce changes in the neuromuscular activity and control of muscles crossing the knee joint (1,9,27). Thus, it seems important to gain knowledge of specific changes in neuromuscular activity profile in meniscectomized patients at high risk of knee OA to design effective interventions to optimize

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knee joint loading and possibly prevent or postpone knee OA development in these patients.

The aim of the current study was to identify differences in knee ROM, movement speed, ground reaction forces (GRF) and neuromuscular activity including muscle coactivation and medial versus lateral muscle activation during stair descent in patients meniscectomized for symptomatic degenerative meniscal tears compared with healthy controls. We hypothesized that patients would display altered patterns of neuromuscular activity including alterations in agonist–antagonist muscle coactivation, accompanied by a decreased range of knee joint motion and reduced movement speed along with reduced GRF to adopt a movement strategy with minimized knee joint loading compared with the nonoperated leg and with healthy controls.

METHODS

Patients, 35–55 yr old at the time of surgery, who had undergone surgery for a medial meniscal tear in the posterior half of the meniscus in the years 2006 and 2007 were identified through the surgical code system from two different hospitals. The age criteria were set to include most patients with degenerative meniscal tears but without knee OA. Patients were excluded if they were misclassified by the surgical code system, if they had had a previous knee ligament injury or severe cartilage changes defined as deep clefts or visible bone at the time of meniscectomy, or if they self-reported comorbidities limiting participation in the study. A modified version of The Self-Administered Comorbidity Questionnaire developed by Sangha et al. (30) was used to identify comorbidities.

The controls (35–55 yr old), from the same geographic region as the patients, were identified through the Danish Civil Registration System. Subjects were excluded if they had had a previous knee ligament injury, knee surgery, or self-reported comorbidities limiting participation in the study. The study aimed at matching patients and controls (i.e., on age and sex) at a group level.

Test procedures. After the informed consent form was signed, knee pain was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) (29) followed by measurements of body height and weight. The KOOS also assesses knee-related quality of life, other symptoms, and function during activities of daily living and during sport and recreational activity. Only scores from the pain subscale are reported in this study. A normalized score is calculated for each subscale (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS has been validated for meniscectomized patients and has shown high test–retest reproducibility (28,29).

After placement of EMG electrodes and electrogoniometers (more details given below), the subjects were asked to descend a four-step staircase at a self-chosen speed, without the use of hand rails and wearing their own comfortable walking shoes. At the bottom of the stairs, subjects continued walking performing a horizontal transition step down onto a force plate imbedded in the floor. The horizontal staircase position was adjusted relative to the position of the force plate so that the length of the horizontal transition step corresponded to one-third of the total leg length for each individual subject (measured from the midpoint of the greater trochanter to the midpoint of the lateral malleolus). Subjects were carefully instructed to continue walking until they reached a cone placed 2 m beyond the force plate. Subjects were allowed two to three stair descent trials for the purpose of familiarization before actual testing. Subsequently, two experimental trials were performed for each leg (i.e., the operated and nonoperated for the patients and the left and the right legs of the controls), and the average of these two trials was used for further analysis. Trials were repeated if visible hesitation, misplaced footing, or stumbles were observed. After the stair descent tests, the subjects conducted three isometric maximal voluntary contraction (MVC) trials for the quadriceps and hamstring muscles, respectively, for the purpose of EMG normalization. The staircase was designed with a rise of 16 cm, a depth of 23 cm, and a step width of 60 cm. The current study had experimental focus on the transition step between stair descent and subsequent level walking because this transition step involves high peak GRF (GRF_{peak}) and thus represents a demanding task for the knee joint during daily walking activities. The order of test leg was randomized for both groups, i.e., operated/nonoperated in the patients and left/right in the controls. In addition to the described test procedures, isokinetic muscle strength was also obtained as previously reported (37). The study was approved by the local ethics committee of the Region of Southern Denmark (ID S-20080044).

Knee angle recordings. A flexible electrogoniometer (Biometrics SG150; Biometrics Ltd., Gwent, U.K.) was placed laterally across both knees of the subjects according to the manufacturer's manual to measure instantaneous knee joint angle during movement. Goniometer data were synchronously recorded with the EMG and force plate signals. During later offline analysis, the instants of foot strike and toe-off were determined from the GRF curve and used as temporal reference points. The goniometer was calibrated with the knee flexed at a 90° angle (0° = full extension).

Force plate analysis. The methods used for data collection and processing are similar to those reported by Larsen et al. (18). In brief, a force plate (Kistler 9281 B; Kistler Instruments, Winterthur, Switzerland) was placed in the floor at a distance of one-third the leg length of the subject from the final step of the stairs to ensure that full foot contact was made as the person stepped down from the last step. The force plate was completely isolated from the staircase structure and the floor to avoid vibration artifacts. The vertical GRF signal (Fz) was recorded at 1000 Hz using a 12-bit A/D converter (DT 3010; Data Translation, Marlboro, MA) (18). Furthermore, two strain gauge–based load cells connected to a custom-made amplifier were integrated in the

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second and fourth steps of the staircase. The duration between contacts on the two load cells (steps) were determined from the load cell signals and used to calculate stride frequency. In the current study, analytical focus was given to the first part of the Fz signal (Fig. 1), which represents the vertical impact phase (i.e., weight acceptance) and thus comprises the phase of energy absorption and GRF_{peak} during ground contact and thus the phase most demanding for the knee joint. All Fz (GRF) signals were normalized as a percentage of body weight (%BW; Fig. 1) and rate of GRF rise during the initial stance phase (loading slope ($Load_{slope}$)) and the GRF_{peak} was calculated. GRF_{peak} occurred in the first half of the Fz signal (Fig. 1: Fz_2). In some cases, an initial force peak (Fz_1) was detected before Fz_2, and if higher than Fz_2, Fz_1 was identified as GRF_{peak}. However, in most cases, Fz_1 was lower than Fz_2. $Load_{slope}$ was defined as the mean rate of Fz rise in percentage of body weight (%BW·s^{-1}) from the instant of foot strike to 80% of GRF_{peak} and reflects the ability to absorb GRF impacts during the initial phase of foot contact. Furthermore, the stride frequency (strides per minute) (S_{freq}), average knee joint velocity (°·s^{-1}) from foot strike to GRF_{peak} (V_{mean}), time from foot strike to GRF_{peak} ($T_{peak\ GRF}$), and time for the entire stance phase (T_{stance}) were determined.

EMG recording and analysis. Bipolar surface EMG signals were obtained from selected knee extensor and flexor muscles (vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), and semitendinosus (ST)) during stair descent and were subsequently normalized to the maximal EMG signal amplitude recorded during an MVC. MVC for the quadriceps and hamstring muscles were performed in a sitting position as maximal isometric extensor or flexor contractions, respectively. The hip was flexed at 90°, and the knee angle was in 60° of extension. Strong verbal encouragement was given during every contraction to promote maximal voluntary effort. EMG signals

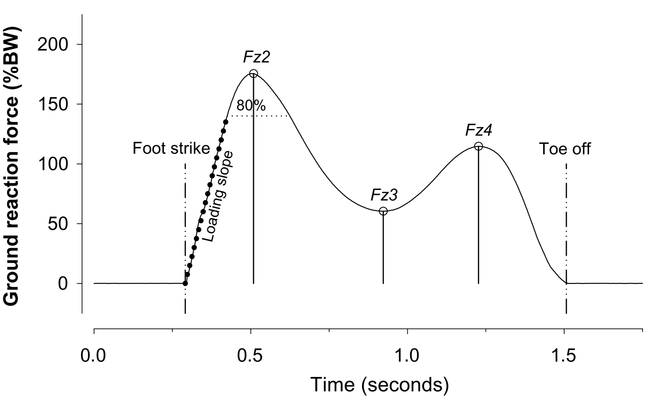

FIGURE 1—Example of M-shaped trajectory (Fz expressed in percentage of body weight) during the stance phase of the transition between stair descent and horizontal walking. Variables are as follows: Fz_2, the first peak force (typically also GRF_{peak}), present in weight acceptance; Fz_3, the minimum force, present during midstance and represents unloading; Fz_4, the second peak force, present in the push-off phase before take-off (Fz_3 and Fz_4 were not analyzed in the present study).

were obtained according to procedures reported elsewhere (18,38) and in agreement with SENIAM recommendations (www.SENIAM.org) using Ag/AgCl surface electrodes (Blue Sensor M, M-00-S/50; Ambu, Ballerup, Denmark) with a 20-mm interelectrode distance. Before placing the electrodes, the skin was shaved and cleaned with alcohol to reduce electrode–skin impedance. EMG electrodes were directly connected to small custom-built preamplifiers taped to the skin. The EMG signals were transmitted through shielded wires to a custom-built differential instrumentation amplifier with a frequency response of 10–10,000 Hz and a common-mode rejection ratio >100 dB. An amplifier gain of 400 (52 dB) was used and included analog high-pass (10 Hz) and low-pass filtering (550 Hz), respectively. Signal-to-noise ratio exceeded 55 dB. All EMG signals were synchronously sampled at a 1000-Hz sampling rate along with the goniometer and force plate signals. During subsequent analysis, any potential DC offset was removed from the raw EMG signals by linear detrending, and subsequently, the signals were digitally high-pass–filtered at the 5-Hz cutoff frequency, followed by full-wave rectification and low-pass filtering at the 10-Hz cutoff frequency (2). All filtering routines used fourth-order zero-lag Butterworth filters. Finally, all EMG signals were normalized to their peak EMG amplitude during MVC. Neuromuscular activity was calculated as the mean normalized EMG amplitude during the loading slope phase (Act_{load}) and at peak GRF ($Act_{peak\ GRF}$; mean in a 20-ms time interval before the instant of GRF_{peak}).

As described by Larsen et al. (18), the magnitude of agonist–antagonist muscle coactivation was calculated as the magnitude of relative normalized signal overlapping (common EMG − signal area) for two EMG signals, namely, EMG_a and EMG_b, relative to the total EMG signal area calculated in a given time interval.

$$\text{coactivation} = \frac{\int \min\{\mathrm{EMG}_a, \mathrm{EMG}_b\}\, dt}{\int \max\{\mathrm{EMG}_a, \mathrm{EMG}_b\}\, dt}$$

Muscle coactivation was calculated for the whole thigh and separately for the lateral and medial parts of the thigh, respectively, during the loading slope phase ($Coact_{load}$: from the instant of foot strike to 80% GRF_{peak}) and at peak GRF ($Coact_{peakGRF}$; mean in a 20-ms time interval before the instant of GRF_{peak}).

In addition, to investigate the distribution of medial versus lateral muscle activity, we also calculated mean medial ((VM + ST)/2) and mean lateral ((VL + BF)/2) neuromuscular activity, respectively, in the leg operated on and nonoperated leg of the patients and for the left/right leg of the controls during the initial weight acceptance phase (loading slope phase) and at GRF_{peak} (mean in a 20-ms time interval before the instant of GRF_{peak}).

Statistical analysis. The Student's unpaired *t*-test and the Mann–Whitney test were used to compare subject characteristics between patients and controls as appropriate. Furthermore, the Student's paired *t*-test was used to

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TABLE 1. Characteristics of subjects.

	Patients (n = 22)	Controls (n = 26)
Subjects, male/female, n	15/7	16/10
Time since surgery (months)	20.7 ± 6.6	N/A
Age (yr)	45.4 ± 5.1	45.6 ± 6.1
Height (cm)	174.3 ± 7.1	174.9 ± 8.1
Weight (kg)	77.3 ± 15.4	78.6 ± 16.8
BMI (kg·m^{-2})	25.4 ± 4.1	25.6 ± 4.7
KOOS, pain	81.0 ± 18.4[a]	97.2 ± 4.6
Self-reported comorbidities		
1–2 musculoskeletal,[b] n	10	9
1–2 general,[b] n	6	6

Values are means ± SD.
[a] Significantly different from controls, $P < 0.001$.
[b] Self-reported comorbidities that subjects were either treated for and/or did not impose any limitation on participation in the study. Musculoskeletal comorbidities reported other than knee problems: joint problems and back pain. General comorbidities reported high blood pressure, diabetes, ulcer, heart problems, and depression.

evaluate differences between medial and lateral muscle activity within the different legs (i.e., operated on, nonoperated, and control legs). A mixed linear model (26) was used to evaluate differences between legs in the kinematic, kinetic, and EMG variables of interest with "subject" as random effect and "leg" (i.e., leg operated on and nonoperated leg for the patients and the left and the right legs of the controls) as fixed effect. If data did not follow the Gaussian distribution, they were log-transformed before analysis but are still presented as non–log-transformed means. Correlation analysis was performed using Spearman ρ to examine the relationship between the magnitude of self-reported pain in patients and the outcome variables obtained in the leg operated on that were significantly different from those of the nonoperated leg or controls. Stata 10.1 (Statacorp, College Station, TX) was used for all statistical analyses, with a prespecified level of significance = 0.05.

RESULTS

A total of 31 patients and 31 controls were ultimately examined. A detailed explanation of the recruitment flow has previously been published (37). Because of equipment malfunction on two consecutive testing days, five patients and five controls had to be excluded from this analysis. Furthermore, four patients reported knee injuries to the contralateral knee (which had previously not been reported). These patients were also excluded. Thus, data are presented for the remaining 22 patients and 26 controls. The characteristics of the participants are shown in Table 1. Patients and controls were similar in all variables, except patients reported more knee pain than controls ($P < 0.001$; Table 1).

Kinematic and kinetic variables. No differences were observed between patients and controls in ROM, movement speed, and GRF variables. However, patients showed a reduced stance phase (T_{stance}) when stepping out on the force plate on the operated leg compared with the nonoperated leg (*post hoc* test, $P = 0.01$). In support, there was a tendency for increased stride frequency (S_{freq}) in trials where patients performed the stair descent transition step using the operated leg compared with the nonoperated leg (Table 2).

Neuromuscular activity and muscle coactivation. No differences were observed in level of activation among the operated, nonoperated, and control legs (Fig. 2). Patients displayed less activity in the medial hamstring muscle (ST) compared with the lateral (BF) hamstrings muscles in the operated and nonoperated legs. This pattern of lower medial versus hamstring muscle activity was also observed in controls. Furthermore, patients showed increased medial (VM) versus lateral (VL) muscle activity at peak GRF ($Act_{peak\ GRF}$) in the nonoperated leg ($P \leq 0.05$), along with a tendency toward reduced medial (VM) versus lateral activity (VL) in the operated leg (Fig. 2). No differences in medial versus lateral muscle activity were observed for the quadriceps muscle in controls. The magnitude of muscle coactivation was similar in patients and controls. However, controls showed a tendency to a higher level of coactivation compared with patients in the medial part of the thigh during the loading slope phase (Fig. 3).

Medial versus lateral leg muscle activity. No differences were observed in mean medial (VM + ST) versus mean lateral (VL + BF) muscle activity among the operated, nonoperated, and control legs (Fig. 4). However, in meniscectomized legs, the mean neuromuscular activity was lower in the medial compared with the lateral thigh muscles during the loading slope phase ($P \leq 0.05$) and at GRF_{peak} ($P \leq 0.01$) (Fig. 4). In contrast, no mediolateral differences in overall thigh muscle activity were observed for the nonoperated leg or in control legs (Fig. 4).

Relationship between patient-reported pain and selected variables. Correlation analysis was performed between KOOS pain score and duration of the stance phase (T_{stance}) and mean medial (VM + ST) muscle activity during the loading slope phase and at GRF_{peak}, respectively. A negative relationship was observed between KOOS pain

TABLE 2. Kinematic and kinetic variables during the transition from stair descent to level walking.

	Patients			
	Operated Leg (n = 22)	Nonoperated Leg (n = 22)	Controls (n = 26, 52 Legs)	P
Knee joint position				
$Angle_{foot\ strike}$ (°)	11.5 ± 1.5	11.4 ± 1.5	10.4 ± 1.2	0.82
$Angle_{toe\text{-}off}$ (°)	54.3 ± 1.40	55.8 ± 1.4	53.7 ± 1.0	0.44
ROM_{stance} (°)	42.9 ± 1.1	44.3 ± 1.1	43.4 ± 0.9	0.42
ROM_{weight} (°)	20.8 ± 1.0	22.4 ± 1.0	21.2 ± 0.8	0.22
Movement speed				
S_{freq} (stride per minute)	68.0 ± 2.8	65.7 ± 2.8	61.6 ± 2.5	0.07
V_{mean} (°·s^{-1})	130.1 ± 10.0	148.5 ± 10.0	138.5 ± 7.4	0.26
$T_{peak\ GRF}$ (ms)	109.4 ± 6.7	107.8 ± 6.7	106.8 ± 5.3	0.94
T_{stance} (ms)	657 ± 22[a]	679 ± 22	677 ± 19	0.04
GRF				
GRF_{peak} (%BW)	163.4 ± 4.8	169.8 ± 4.8	160.3 ± 4.0	0.12
$Load_{slope}$ (%BW·s^{-1})	1966 ± 161	2135 ± 161	1904 ± 136	0.32

Values are means ± SE; mixed linear model. P value indicates main effect of "leg". $Angle_{foot\ strike}$, knee angle at foot strike; $Angle_{toe\text{-}off}$, knee angle at toe-off; GRF_{peak}, peak GRF; $Load_{slope}$, loading slope; ROM_{stance}, difference between knee angle foot strike and toe-off, range of motion during stance phase; ROM_{weight}, difference between knee angle foot strike and maximal knee flexion during weight acceptance, range of motion during weight acceptance; S_{freq}, stride frequency; $T_{peak\ GRF}$, time foot strike to peak GRF; T_{stance}, time entire stance phase; V_{mean}, knee angular velocity from foot strike to peak GRF.
[a] Significant difference between the operated and nonoperated leg of the patient, *post hoc* test, $P \leq 0.05$.

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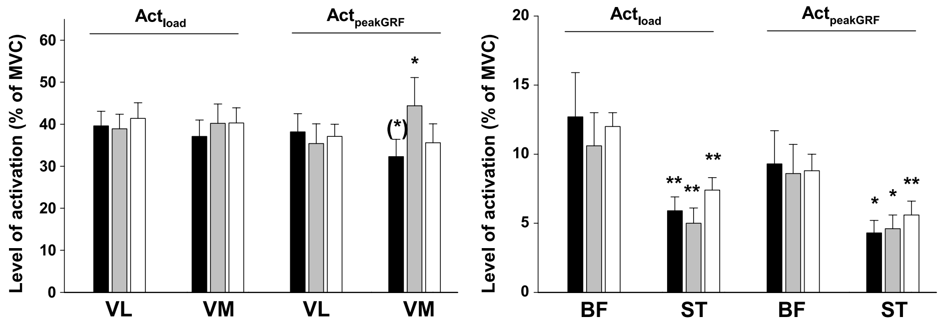

FIGURE 2—Level of activation in percentage of MVC measured in the transition phase between stair descent and level walking for the operated leg (*black bars*) and nonoperated leg (*gray bars*) of the patients and the left/right leg of the controls (*white bars*), during the loading phase (Act$_{load}$) and at peak GRF (Act$_{peak\ GRF}$; mean in a preceding 20-ms time interval) for the vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), and semitendinosus (ST). Values are means ± SE. *Significantly different from lateral side (VL or BF), $P \leq 0.05$. **Significantly different from lateral side (VL or BF), $P \leq 0.01$. (*) Tendency for difference compared with lateral side (VL or BF), $0.05 \leq P \leq 0.10$.

and T_{stance} ($r_s = -0.47$, $P = 0.03$), whereas no relationship was observed between self-reported pain and medial muscle activity.

DISCUSSION

The aim of the current study was to examine whether altered patterns of neuromuscular activity and agonist–antagonist muscle coactivation could be identified in middle-aged meniscectomized patients at high risk of future knee OA between the operated and nonoperated legs and compared with healthy controls. Such alterations could potentially affect knee joint kinetics and kinematics and hence influence the development of OA. We did not observe the hypothesized differences between patients and controls, but we observed a shorter stance phase (T_{stance}) in the meniscectomized leg compared with the nonoperated leg in patients. Furthermore, lower neuromuscular activity was observed in the medial (mean VM + ST) compared with the lateral (mean VL + BF) thigh muscles in the meniscectomized leg of patients. This may represent early changes in neuromuscular control in the initial state of knee OA development.

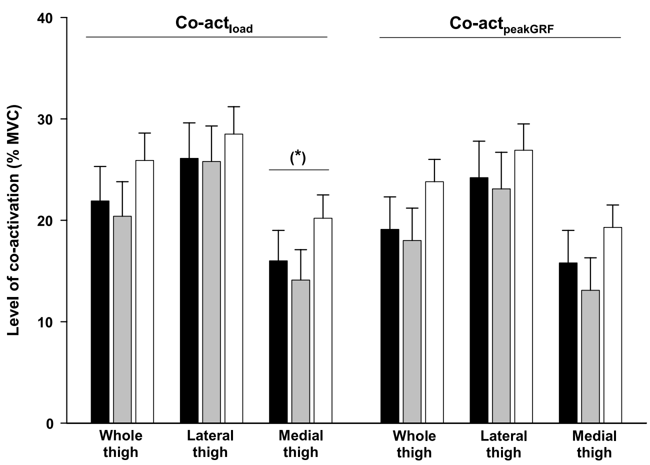

FIGURE 3—Level of coactivation for the operated leg (*black bars*) and nonoperated leg (*gray bars*) of the patients ($n = 22$) and the left/right leg of the controls ($n = 26$) (*white bars*), during the loading slope phase (Coact$_{load}$) and at peak GRF (Coact$_{peak\ GRF}$; mean in a preceding 20-ms time interval) calculated for the whole thigh (VM + VL vs BF + ST), lateral part of the thigh (VL vs BF), and the medial part of the thigh (VM vs ST). Values are means ± SE. (*) Tendency for the main effect of "leg" among operated, nonoperated, and control legs, $0.05 \leq P \leq 0.10$.

Previous studies on patients with knee OA have reported increased levels of leg muscle coactivation (14,15,19,32), altered medial versus lateral muscle activation (11,16,17), and increased knee adduction moment (3,19) during gait and stair ascent/descent. It is not clear whether these changes are a consequence of knee OA or precede the disease. Several studies have been conducted on the biomechanics of gait and stair ascent/descent (4,6,21,22,35,36) and changes in neuromuscular activity (6,10,21,22) in meniscectomized patients. However, the above studies either involved younger patients with traumatic meniscal tears (4,6,21,22) and/or patients soon after surgery, thus representing early postsurgical recovery (6,10,22,35,36). Observed deficiencies, therefore, might not only have been due to the meniscal tear *per se* but may also have been due to the surgical procedure itself (6,22,35,36). In the current study, middle-aged patients were examined ~21 months after meniscectomy of degenerative tears to represent patients in a "preosteoarthritis" state (7,8) while considered to be fully rehabilitated after surgery.

In contrast to our expectations, no differences in any knee joint kinetic and kinematic variables were observed between patients and controls. Likewise, no differences emerged in knee ROM (ROM$_{stance}$ and ROM$_{weight}$), knee joint position (Angle$_{foot\ strike}$ and Angle$_{toe\text{-}off}$), or GRF between the operated and nonoperated legs of the patients (Table 2). Nevertheless, a reduced T_{stance} (~3%) was observed in meniscectomized legs compared with nonoperated legs. Thus, our hypotheses of an altered kinetic and kinematic profile in meniscectomized patients were only partially confirmed by the current data, but differences were only evident between the operated and nonoperated legs of the patients. The finding of a 3% reduced T_{stance} during the stair-to-ground transition phase in the meniscectomized leg compared with nonoperated leg is probably of limited clinical significance, although it potentially reflects a greater

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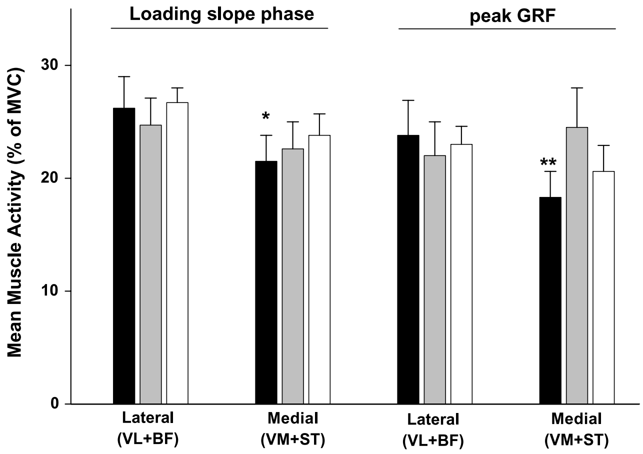

Figure 4—Lateral (VL + BF) versus medial (VM + ST) mean muscle activity for the operated leg (*black bars*) and nonoperated leg (*gray bars*) of the patients ($n = 22$) and the left/right leg of the controls ($n = 26$) (*white bars*) during initial weight acceptance (loading slope phase) and at GRF_{peak} (mean in a preceding 20-ms time interval). Values are means ± SE. Significant difference compared with mean lateral muscle activity, *$P \leq 0.05$, **$P \leq 0.01$.

reliance on the unaffected limb during stair descent. However, the finding of a negative relationship between pain and the duration of the stance phase in the operated leg (i.e., more pain was associated with a longer stance phase) indicates that a useful strategy to minimize pain during stair descent in this population is by producing a given amount of kinetic impulse (momentum) using an extended time of contact (t) and thereby reduce the magnitude of contact force (F) exerted in the knee joint (since Δmomentum = Ft). Thus, the above relationship may be a sign of pain contributing to an asymmetric movement pattern in an attempt to reduce knee joint load.

It was expected that meniscectomized patients would demonstrate altered patterns of neuromuscular control including increased muscle coactivation, which have been suggested to affect knee ROM. However, contrary to our expectations, knee ROM did not differ between patients and controls, but patients tended to have lower muscle coactivation in the medial part of the thigh than controls during the weight acceptance phase (Fig. 3).

In the current study, neuromuscular activity was generally lower (~50%) in the medial (ST) versus lateral (BF) hamstring muscles in both legs of the patients. A similar pattern was observed in controls (~40% lower medial activity), indicating that this represents a general and normal pattern of hamstring activity during stair descent (Fig. 2). Clinicians often observe medial quadriceps (VM) atrophy and neuromuscular deficits after knee injury and delayed VM versus VL muscle activity onset has been reported in patients with patellofemoral pain (5). Our results seems to support this notion because neuromuscular activity tended to be lower in the medial (VM) compared with the lateral (VL) quadriceps in meniscectomized legs at GRF_{peak}.

The current study also investigated the distribution of overall medial versus lateral muscle activity because skewed patterns of medial versus lateral muscle activity could potentially affect knee control/function and joint stability. No differences were observed between mean medial (VM + ST) and mean lateral (VL + BF) muscle activity among the operated, nonoperated, and control legs. However, we observed reduced (~20%) medial compared with lateral mean muscle activity in meniscectomized legs. In contrast, no differences in medial versus lateral muscle activity were observed in the nonoperated legs of patients or in controls. Increased levels of lateral muscle activity have previously been observed in patients with knee OA compared with controls (11,16), increasing with OA severity (17). This likely represents a neuromuscular strategy to reduce knee adduction moment and decrease medial knee joint compartment loading (11). Thus, the reduction in medial muscle activity currently observed in meniscectomized legs could reflect a strategy to decrease compression forces in the medial compartment of the knee joint. The specific effect of attenuated medial muscle activity on biomechanical knee joint loading profile and specifically on the knee adduction moment, which is often used as a surrogate measure for medial knee compartment joint loading (24,31,40) and is associated with medial knee OA severity (33), currently remains unknown. Recently, Netravali et al. (23) reported that patients meniscectomized for medial meniscal tears in the posterior part of the meniscus (similar to the present patients) showed increased external rotation of the tibia throughout the stance phase during walking. The presence of such a gait pattern is likely to affect knee joint stability and could be an alternative explanation for the altered medial versus lateral muscle activity in the meniscectomized legs in this study.

The patients examined in the current study self-reported elevated levels of knee pain compared with population-based controls. Increased pain feedback may be a contributor to the reduced medial muscle activity. Pain has also been suggested to be a contributing factor in arthrogenic muscle inhibition (AMI) (25) resulting in reduced motor drive to the muscles surrounding an injured joint (13). Henriksen et al. (12) recently reported reduced levels of muscle activity in response to experimentally induced VM muscle pain during a forward lunge. However, in the present study, we observed no relationship between pain and reduced medial muscle activity indicating that pain was probably not the main cause of the observed alterations in neuromuscular activity during stair descent.

We recently reported no differences in maximal muscle strength between the operated and nonoperated legs of the same patients as the present study (37), indicating that changes/asymmetries in neuromuscular activity potentially precede the occurrence of future strength deficits/asymmetries in this population of patients. In the current study, the relatively modest limb-to-limb differences observed in patients may be due to the relatively short time interval between surgery and testing (i.e., ~2 yr), and thus, the potential development of knee OA may not have progressed as much as in patients studied at later time points. Furthermore, this may also explain the current lack of gross systematic differences in neuromuscular activity and kinetic gait profile between patients and controls since early changes may manifest first as asymmetries between the operated and nonoperated leg of the patients, potentially leading to bilateral differences at more progressed stages toward knee OA.

The current study has limitations. First, this was a cross-sectional study. Thus, the underlying cause of the observed changes and the effect on knee OA development remains speculative. Second, in the current study, we used GRF as an indicator of knee joint loading; however, this measure may not reflect the actual magnitude of bone-on-bone contact forces exerted in the knee joint. Third, five patients and five controls were excluded because of equipment malfunction. These participants may have performed differently from the included participants. However, this is unlikely because both the excluded patients and the controls were highly similar to the rest of the participants (i.e., age, height, weight).

CONCLUSIONS

The hypothesized reduction in knee ROM, movement speed, and altered GRF kinetics and neuromuscular activity between patients and controls could not be confirmed. However, we observed a shorter stance phase in meniscectomized legs during the transition step between stair descent and level walking along with lower medial leg muscle activity in the meniscectomized leg. These findings support the hypothesis that meniscectomized patients demonstrate early modulations in kinematics and neuromuscular activity, which may represent a strategy to reduce knee joint pain. Further, the present study findings also indicate that training/rehabilitation of meniscectomized patients should focus also on neuromuscular control of the hamstring and quadriceps muscles and not rely entirely on muscle strength development alone. The current findings may represent an initial stage in the possible chain of events leading to knee OA in meniscectomized patients. The exact mechanisms of these changes and their effect on knee adduction moment and knee OA development remain unknown and warrant further investigation. Future studies should examine whether the observed biomechanical and neuromuscular changes are exacerbated in patients with a longer postsurgery time interval (i.e., representing patients at a more progressed state of knee OA development).

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Paper III

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Muscle strength and functional performance in patients at high risk of knee osteoarthritis: A Follow-up Study

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ABSTRACT

Purpose: To investigate if changes from 2 to 4 years post arthroscopic partial meniscectomy (APM) in mechanical muscle function and objectively measured function differ between the operated and contra-lateral leg of APM patients or compared with controls.

Methods: Twenty-two patients (age 46.6±5.0, BMI 24.7±2.9) and 25 controls (age 46.4±5.2, BMI 25.1±4.6) previously examined at ~2 years post APM were examined again at ~4 years post surgery for maximal knee extensor/flexor voluntary contraction (MVC) and rapid force capacity. Functional performance was assessed by the distance achieved during a one-leg hop test and the maximum number of knee bends performed in 30 seconds. The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to evaluate self-reported outcomes.

Results: Overall changes from 2 to 4 years post APM did not differ in maximal muscle strength, rapid force capacity and functional performance between the operated and contra-lateral leg of patients or control legs. However, secondary analysis showed a difference in change in knee extensor MVC resulting in a 6% difference between the operated and contra-lateral leg of patients at follow-up.

Conclusions: No differences in longitudinal changes were observed from 2 to 4 years post APM between patients and controls. The secondary finding of differential changes over time in knee extensor MVC between the operated and contra-lateral leg partly confirm our hypothesis that differences in muscle strength may evolve from 2 to 4 years post APM. This differential change may represent an initial sign of an evolving lower limb muscle asymmetry, which may play a role in the development of knee OA.

INTRODUCTION

Patients undergoing arthroscopic partial meniscectomy (APM) constitute a sub-group of patients with a high risk of developing knee osteoarthritis (OA) [9, 11, 21]. Studies have shown that approximately half of the patients show radiographic signs of knee OA 10-15 years after meniscectomy [11, 26, 27]. Meniscus tears are often categorized as either traumatic or degenerative tears. Traumatic tears are typically observed in an otherwise 'healthy' meniscus of younger active individuals in relation to a sports related trauma [22]. Degenerative tears are observed in the middle-aged (35-55 years) and older population and are described as horizontal cleavages, flap tears or complex tears but the etiology is unclear [22]. Degenerative meniscus tears have been suggested to be associated with incipient OA and/or represent early-stage OA in the middle-aged population [8, 10]. Thus, patients undergoing meniscus surgery for symptomatic degenerative tears constitute a model to study the state prior to knee osteoarthritis.

Reduced muscle strength has been suggested as one of the modifiable risk factors for knee OA [17, 28, 29, 39]. Previous studies of maximal muscle strength in meniscectomized patients have reported large short-term (0-6 months) fluctuations and different levels of recovery [7, 15, 16, 20, 31-33]. However, previous study populations have been rather heterogeneous including patients with different combinations of medial/lateral and traumatic/degenerative meniscus tears making data interpretation difficult. Furthermore, short-term recovery (0-6 months) may primarily be a sign of recovery from the surgery induced trauma rather than reflecting recovery from the meniscus tear *per se*.

Various aspects of mechanical muscle function and self-reported pain and function have recently been investigated in a homogenous group of patients ~2 years after surgery for medial symptomatic degenerative meniscus tears [36]. Despite patients self-reporting pain and reduced function no differences in mechanical muscle function were observed in the operated leg compared with the contra-lateral leg or when compared with population-based controls [36]. In contrast, two previous studies with similar patients reported a bilateral difference >20% in maximal muscle strength between patients and controls [4] and a moderate difference of ~9% in muscle strength and objectively measured function between the operated and the contra-lateral leg 4 years post APM [13].

These discrepancies in muscle strength deficits between studies may be explained by differences in post-surgery time intervals and thus the potential development of knee OA may not have progressed as dramatically at 2 years vs. 4 years post APM.

The aim of the present follow-up study was to investigate if changes from 2 to 4 years post APM in maximal muscle strength, rapid force capacity and objectively measured function would differ between the operated and contra-lateral leg of patients or compared with population-based controls. It was hypothesized that differences would evolve in maximal muscle strength, rapid force capacity and objectively measured function from 2 to 4 years post APM between the operated and contra-lateral leg and compared to controls. Deterioration in muscle strength and functional performance between years 2 and 4 post APM could reveal a potential window of opportunity for knee OA prevention strategies.

MATERIALS AND METHODS

Details about the baseline recruitment process, flow chart and inclusion/exclusion criteria at 2 years post APM have previously been reported [36]. In short, patients 35-55 years old at time of surgery, who had undergone APM for a medial meniscus tear in the posterior half of the meniscus in the years 2006 and 2007 were identified through the surgical code system from two different hospitals. The age criteria was set to include a majority of patients with degenerative meniscus tears but without knee OA. Exclusion criteria; misclassified by the surgical code system, previous knee ligament injury, severe cartilage changes defined as deep clefts or visible bone at APM and self-reported co-morbidities limiting participation in the study. Age and gender matched controls from the same geographic area as the patients, were identified through the Danish Civil Registration System. Exclusion criteria; previous knee surgery and/or ligament injury and self-reported co-morbidities limiting participation in the study.

All participants included at baseline (31 patients and 31 controls) received a written invitation to participate in the follow-up examination. If participants failed to reply to the invitation they were contacted by phone. The baseline and follow-up examination were conducted 21.6±5.1 and 49.6±5.0 (means±SD) months following time of APM, respectively.

Outcome measures

Muscle strength testing

Following a standardized warm-up and preconditioning procedure, maximal voluntary isometric contraction strength (MVC) was measured in an isokinetic dynamometer

(KinCom; Kinetic Communicator 500H, Chattecx Corp., Hixson, TN, USA) for the knee extensors and knee flexors at a 70˚ knee joint angle (0º=full knee extension, best of three trials) according to previously published procedures [1, 36, 37]. The dynamometer force signal was recorded as previously reported [36, 37], and multiplied with the lever arm (i.e. the distance from the axis of rotation to the fore transducer) to calculate joint torques (N m). All measurements were corrected for the effect of gravity [2] and normalized to body mass [5]. Visual feedback of the dynamometer torque output was provided to the subjects on a computer screen after each trial [18]. The reliability and validity of the KinCom dynamometer have previously been verified in detail elsewhere [14, 30].

In addition, the average slope (Δtorque/Δtime) at time points 0-30, 50, 100 and 200 milliseconds (ms) (0 ms = onset of contraction) of the torque-time curves were analyzed to evaluate the capacity for rapid force production (i.e. rate of force development – RFD) in the initial phase of contraction. These time intervals have previously been used to assess RFD in the initial phase of muscle contraction in healthy [1, 37] as well as in surgical patients [34].

Functional capacity tests

Two tests, the one-leg hop test [35] and the maximal number of single-legged knee bends subjects were able to perform within 30 s [23] were used to assess functional performance. Both tests have previously been shown to be valid and reliable in meniscectomized patients [6]. Testing procedures where identical to the baseline assessment [36].

The operated and the contra-lateral leg of the patients as well as the left and right leg of the controls, were assessed during muscle strength and functional capacity testing.

Self-reported outcomes

The Knee Injury and Osteoarthritis Outcome Score (KOOS) was filled out prior to all other measurements and physical tests. The KOOS is a knee specific questionnaire used to assess knee related pain, symptoms, function during activities of daily living (ADL) and sport and recreation function (Sport/Rec) as well as quality of life (QOL) [25]. A normalized score is calculated for each subscale (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS score has been validated for meniscectomized patients and has shown high test-retest reproducibility [24, 25].

Other descriptive measures:

At baseline, anthropometrics and hand grip strength were measured and maximal oxygen uptake was estimated using Åstrands Nomogram [3] as previously described [36]. Informed consent form was signed at baseline and follow-up and the study procedures were approved by the ethics committee of the Region of Southern Denmark (ID: S-20080044). All procedures were identical at both examinations and the order of test-leg was randomized for both groups (i.e. operated/contra-lateral in the patients and left/right in the controls). The examiner was not blinded to group allocation (i.e. patient/control) but patients wore non-supportive knee bandages on both legs to conceal which leg was the operated leg.

Statistical analysis: Students unpaired t-test and chi-squared test were used as appropriate to compare baseline characteristics of patients and controls that completed all examinations at both time points.

The Mann-Whitney test was used to assess differences in self-reported outcomes (i.e. KOOS scores) between patients and controls at follow-up and between participants (i.e. patients and controls, respectively) included in the present analyses and those who did only reply the questionnaires.

No differences were detected between the left and right leg of the controls in any of the physical tests. Thus, left and right legs were collapsed into 'control legs'. To detect differences in changes between the operated, contra-lateral and control legs in maximal knee extensor/flexor strength and functional performance mixed linear models were used with 'subject' as random effect and 'leg' (i.e. operated, contra-lateral and control legs) as fixed effect. Changes in RFD at 0-30, 50, 100 and 200 ms, respectively were analyzed using a mixed linear model with 'subject' and 'side' as random effects (i.e. repeated nested measurements on each leg of the subjects) and 'leg' as fixed effect. The variable 'side' was added to the analysis to account for the within leg variation between the left/right legs of controls. All models were adjusted for baseline values and age and sex were introduced as covariates in the model to adjust for potential confounding.

Stata 10.1 (Statacorp, College Station, TX, USA) was used for all statistical analyses, using a pre-specified level of significance = 0.05.

RESULTS

Four patients (2 men/2 women) and 3 controls (3 men) had dropped out at the follow-up examination (Patients: 1 due to back injury, 3 unable to contact; Controls: 2 due to lack of time, 1 unable to contact). Overall, no differences were observed in characteristics (age, BMI and VO_2-max) of patients (n=4) and controls (n=3) that dropped out compared to those who were available for follow up at 4 years post APM. However, controls that dropped out demonstrated a higher hand grip strength (51.5±7.3 vs. 36.6±7.7 kg [means±SD], $p=0.003$).

Furthermore, 5 patients (1 man/4 women) and 3 controls (2 men/1 woman) were only able/willing to reply the KOOS questionnaire and did not participate in the physical examination (Patients: 1 moved to another country, 1 due to back injury, 1 due to depression, 1 scheduled for knee replacement, 1 due to recent surgery for hernia; Controls: 2 due to lack of time, 1 due to joint pain). Patients that only answered the questionnaire (n=5) self-reported more pain (78.3±12.3 vs. 90.3±13.2 [means±SD], $p=0.03$), more symptoms (71.4±13.1 vs. 90.7±10.1, $p=0.004$), impaired ADL (82.1±12.8 vs. 94.5±9.4, $p=0.03$) and reduced Sport/Rec function (45.0±33.0 vs. 84.5±20.8, 0.01) together with a tendency towards reduced QOL (57.5±27.0 vs. 78.7±16.7, $p=0.08$) than patients completing the 4 year follow up (n=22). Contrary, there were no difference in any KOOS subscale scores between controls participating in the physical examination (n=25) and those who only replied the questionnaire (n=3).

Data for the remaining 22 patients and 25 controls are used in the analysis in the present study. No differences were observed in any of the baseline characteristics between patients and controls except for hand grip strength (Table 1).

Maximal muscle strength, RFD and functional performance

At the baseline examination no differences were observed between the operated and contra-lateral legs of patients or when compared with controls in maximal isometric knee extensor/flexor strength, overall RFD or functional performance (Table 2).

A tendency towards a difference in change from baseline to follow-up was observed between the operated, contra-lateral and control legs in knee extensor MVC ($p=0.09$). Secondary analysis showed a significant difference ($p=0.04$) in change in knee extensor MVC from baseline to follow-up when comparing only the operated and contra-lateral legs of patients. No differences in change were observed between the operated, contra-lateral and control legs in knee flexor MVC or functional performance (Table 2).

No differences in change from baseline to follow-up were observed in overall RFD of the knee extensors (Table 3) or flexors ($p>0.34$, data not shown) between the operated, contra-lateral and control legs.

Self-reported outcomes

At follow-up 4 years post APM patients self-reported reduced knee related QOL compared with controls (78.7±3.6 vs. 90.0±2.7, $p=0.007$). Furthermore, there was a tendency towards patients self-reporting more pain ($p=0.08$) and symptoms ($p=0.08$) compared to controls whereas no differences were observed in self-reported function (i.e. ADL and Sport/Rec ($p>0.18$) (Figure 1).

DISCUSSION

The primary finding of the present study was that no overall differences were observed in change over time between patients meniscectomized for degenerative medial meniscus tears and population-based controls in maximal muscle strength, rapid force capacity and functional performance from 2 to 4 years post surgery. However, secondary analysis showed a difference in change over time in patient knee extensor MVC, manifested as an increase in the contra-lateral leg compared with the operated leg, from 2 to 4 years post APM.

Previous knee injury and impaired muscle strength are considered risk factors for knee OA [19, 28, 29]. A recent study was unable to detect differences in mechanical muscle function between meniscectomized patients considered to be in a "pre-OA" state and population-based controls 2 years post APM [36]. Yet, two previous studies have reported reduced muscle strength in similar patients 4 years post surgery [4, 13]. Thus, this follow-up study was conducted to investigate if strength deficits could evolve between years 2 and 4 post meniscectomy and potentially represent a window of opportunity for interventions to retain strength and potentially slow the development or decrease the risk of knee OA in these patients. No significant differences were observed in longitudinal changes from baseline to follow-up in maximal knee flexor muscle strength, overall rapid force capacity (i.e. RFD) of the knee extensors and flexors or functional performance between the operated and contra-lateral leg of patients or compared with controls. However, a tendency towards a difference in change from baseline to follow-up was observed between the operated, contra-lateral and control legs in knee extensor MVC ($p=0.09$). Secondary analysis revealed a significant difference ($p=0.04$) in change in knee extensor MVC from baseline to follow-up resulting in a 6% difference between the operated and contra-lateral leg of patients at follow-up. The observed difference in change was caused by an increase in contra-lateral leg MVC rather than reduced strength of the operated leg. This may be due to increased dependence on the contra-lateral leg. In support of this notion, we recently reported a reduced stance phase in the operated leg compared to the contra-lateral leg in meniscectomized patients during stair descent indicating greater reliance on the un-injured limb [38]. The finding of a 6% difference between legs is in line with the findings by Ericsson et al. [13] reporting modest differences of 6-9% in maximal knee extensor torque between the operated and contra-lateral leg 4 years post meniscectomy. In contrast, Becker et al. [4] reported a bilateral strength deficit >20% between meniscectomized patients and controls. This discrepancy may be caused by differences in selection of patients/controls. Thus, recruitment per se could be suspected to be a major factor for the divergent results on muscle strength deficits in APM patients. The recruitment process is often sparsely reported. Patient recruitment from a clinical setting or by advertisement may introduce selection bias towards patients with more severe symptoms. In the present study, great care was taken during the initial recruitment process to ensure that patients were representative of a population who had undergone meniscectomy for a degenerative tear [36]. In the study by Becker et al. [4] no information was given on patient recruitment procedures. In addition, none of their patients were engaged in sports or exercise activities and no information on participation in sports was provided for their control subjects. Thus, the reported difference in muscle strength (i.e. >20%) in the study by Becker et al. [4] between patients and controls might be influenced by a higher level of physical activity in the control group. In the current study general muscle strength (hand grip strength) and general fitness (VO_2-max) (i.e. surrogate measures of physical activity) were similar in patients and controls at time of recruitment indicating similar levels of physical activity [36].

A recent study have previously reported initial changes in neuromuscular activity pattern of selected leg muscles between the operated and contra-lateral leg during stair descent 2 years post APM [38] although no differences in maximal muscle strength were observed [36]. The present observation of differential longitudinal changes in knee extensor MVC partly confirm the hypothesis that deficits in muscle strength may evolve between the operated and contra-lateral leg from 2 to 4 years post APM. Although small in number, the literature supports the clinical relevance. Hootman et al. [17] reported baseline deficits of 7 and 9% in knee extensor strength in men and women, respectively, of similar age as in the present study, self-reporting knee or hip OA 14 years later compared to those who did not. These findings indicate that impairments in muscle strength prior to knee OA may be subtle and that the observed differential change, and evolving asymmetry over time may be an early sign of changes in knee extensor muscle strength prior to knee OA, where especially quadriceps muscle strength has been suggested to play a role [28, 29]. Thus, the present findings suggest that monitoring leg-to-leg differences in muscle strength over time in the clinic may be important since such differences could be targeted with training interventions which have previously shown to be effective for this type of patients [12].

In the present study patients self-reported worse quality of life together with a tendency towards more pain and symptoms compared to controls. KOOS sub scores however indicated less problems at 4 years post APM compared to 2 years post APM [36] and also when compared to data by Ericsson et al. [13] 4 years post meniscectomy. Patients not performing the physical test but only replying the KOOS questionnaire self-reported worse on all subscales compared to those patients who completed the physical tests, which might explain this discrepancy. The fact that patients not performing the physical tests self-reported worse on all sub scales of the KOOS could potentially decrease the likelihood of detecting differences between the operated and contra-lateral leg of patients or compared with controls. To take this into account, all statistics on muscle strength variables and functional performance were adjusted for values at 2 years post meniscectomy. No difference in KOOS scores were observed between those controls that participated in the physical examination compared to those who only replied to the questionnaire.

The current study has limitations. Due to the strict inclusion/exclusion criteria to include a majority of patients with degenerative tears the present results and conclusions may only apply to these patients and cannot be generalized to younger patients with traumatic tears. Further, drop out of patients and controls occurred from the first to the second assessment (i.e. 4 patients and 3 controls). However, physical characteristics (age, BMI and VO_2-max) did not differ between patients (n=4) and controls (n=3) that dropped out compared to those who stayed in the study except that drop out controls showed a higher hand grip strength than control subjects who stayed in the study. Finally, study groups (i.e. patients and controls) were not exactly matched with respect to sex at time of recruitment and due to drop outs this distribution got even more skewed at the follow-up examination. Even though chi-squared test showed no statistically significant difference in the distribution of men and women in the two groups (p=0.13) all strength and functional performance variables were adjusted for age and sex.

CONCLUSION

Longitudinal changes in knee flexor MVC, knee extensor/flexor RFD and functional performance in the time span from 2 to 4 years post meniscectomy were similar in operated and contra-lateral legs of patients and legs of population-based controls. However, secondary analysis revealed differential changes in knee extensor MVC between the operated and contra-lateral leg, manifested as increased contra-lateral leg strength, partly confirming our hypothesis that differences in muscle strength may evolve from 2 to 4 years post APM. This differential change may represent an initial sign of an evolving lower limb muscle asymmetry, which may play a role in the development of knee OA.

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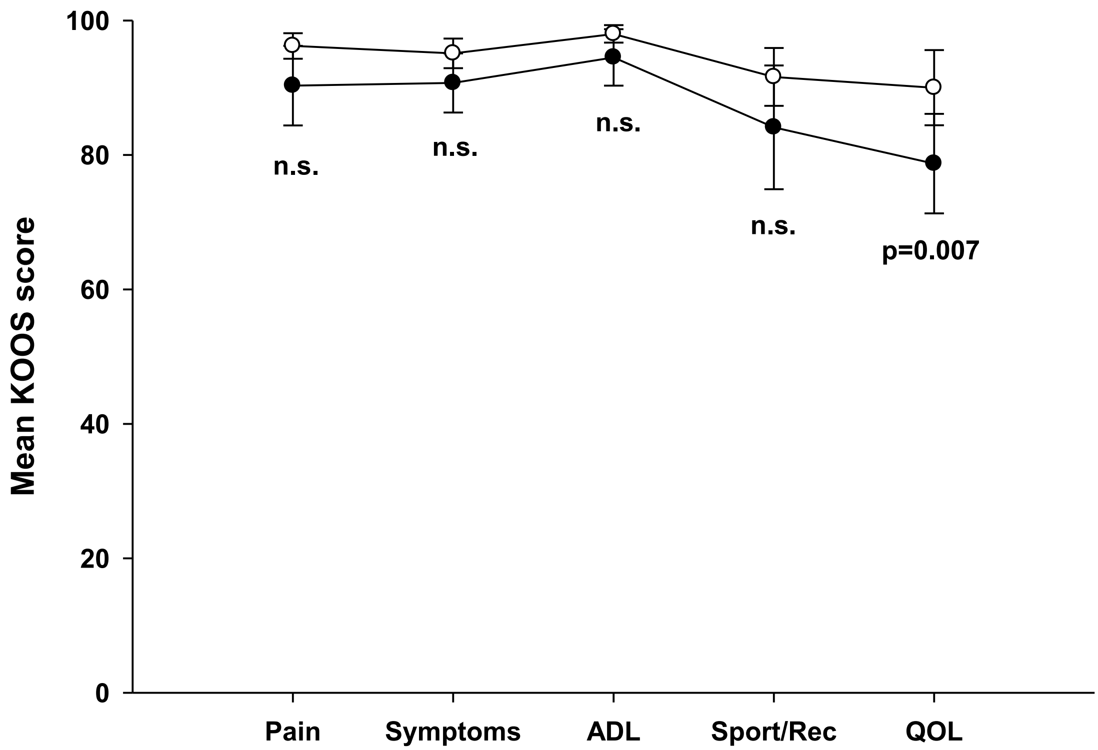
FIGURE LEGENDS:

Figure 1: Knee Injury and Osteoarthritis Score (KOOS) results at 4 years post meniscectomy for the patients (solid circles) and controls (open circles). Results are means with 95% confidence intervals presented as an outcome profile of the 5 dimensions of the KOOS scale. A score of 100 represents no knee problems and a score of 0 represents extreme problems. ADL=activities of daily living, Sport/Rec=sport and recreational function, QOL=quality of life.

FIGURE 1:



100
80
60
40
20
0
Mean KOOS score
n.s.
n.s.
n.s.
n.s.
p=0.007
Pain
Symptoms
ADL
Sport/Rec
QOL

Table 1: Characteristics of participants at baseline (2 years post meniscectomy)

	Patients	Controls	*P*
Subjects, no. (male/female)	22 (17/5)	25 (14/11)	0.13
Time since surgery (months)	21.6 ± 5.1	N/A	
Age (years)	46.6 ± 5.0	46.4 ± 5.2	0.88
BMI (kg/m^2)	24.7 ± 2.9	25.1 ± 4.6	0.70
VO_2-max (ml $O_2 \cdot kg^{-1}$)	37.9 ± 8.2	35.9 ± 9.5	0.44
Hand grip strength (kg)	41.4 ± 7.8	36.7 ± 7.4	0.04

Values are means ± SD.

Table 2: Maximal muscle strength and functional performance at baseline (2 years post meniscectomy) and change from baseline to follow-up (4 years post meniscectomy) for the operated leg (n=22), contra-lateral leg (n=22) and control legs (50 legs, n=25).

	Baseline, un-adjusted mean (SD)				**Change from baseline assessment, mean adjusted for baseline assessment, age and sex (95% CI)**			
	Operated leg	**Contra-lateral leg**	**Controls legs**	***p*-value***	**Operated leg**	**Contra-lateral leg**	**Controls legs**	***p*-value****
Knee extensor MVC (Nm*kg^{-1})	2.91 (0.60)	2.93 (0.54)	2.60 (0.43)	n.s.	0.01 (-0.16-0.18)	0.19 (0.02-0.37)	0.04 (-0.10-0.18)	n.s.
Knee Flexor MVC (Nm*kg^{-1})	1.20 (0.21)	1.27 (0.23)	1.18 (0.28)	n.s.	0.06 (-0.02-0.14)	0.06 (-0.02-0.15)	0.05 (-0.02-0.12)	n.s.
Knee bends/ 30 s (no.)	27.2 (9.6)	26.9 (8.4)	29.8 (10.8)	n.s.	5.0 (2.7-7.3)	4.0 (1.8-6.3)	3.9 (1.8-6.0)	n.s.
One-leg hop (cm)	92.4 (20.0)	91.5 (19.7)	90.5 (23.4)	n.s.	3.5 (-1.9-9.0)	5.3 (-0.2-10.8)	-0.8 (-5.4-3.7)	n.s.

* Mixed linear model adjusted for age and sex. P-value indicate main effect of 'leg'
** Mixed linear model adjusted for baseline assessment, age and sex. P-value indicate main effect of 'leg'
CI, confidence interval; MVC, Maximal Voluntary Contraction

Table 3: Rate of force development (RFD) for the knee extensors in the time intervals 0-30, 50, 100 and 200 at baseline (2 years post meniscectomy) and change from baseline to follow-up (4 years post meniscectomy) for the operated leg (n=22), contra-lateral leg (n=22) and control legs (50 legs, n=25).

	Baseline, un-adjusted mean (SD)				Change from baseline assessment, mean adjusted for baseline assessment, age and sex (95% CI)			
	Operated leg	**Contra-lateral leg**	**Controls legs**	***p*-value***	**Operated leg**	**Contra-lateral leg**	**Controls legs**	***p*-value****
0-30 ms ($Nm*s^{-1}*kg^{-1}$)	12.6 (6.7)	14.1 (6.0)	10.4 (4.2)	n.s.	2.6 (0.3-4.9)	2.5 (0.1-4.8)	3.0 (1.3-4.6)	n.s.
0-50 ms ($Nm*s^{-1}*kg^{-1}$)	15.8 (7.0)	16.4 (6.3)	13.3 (5.0)	n.s.	1.9 (-0.2-4.1)	2.9 (0.8-5.1)	2.5 (1.0-4.0)	n.s.
0-100 ms ($Nm*s^{-1}*kg^{-1}$)	14.7 (4.1)	14.4 (4.4)	13.0 (3.1)	n.s.	1.0 (-0.3-2.3)	2.3 (1.0-3.6)	0.8 (-0.3-1.8)	n.s.
0-200 ms ($Nm*s^{-1}*kg^{-1}$)	10.2 (2.4)	10.1 (2.7)	9.0 (1.8)	n.s.	0.6 (-0.3-1.4)	1.2 (0.4-2.1)	0.4 (-0.3-1.1)	n.s.

* Mixed linear model adjusted for age and sex. P-value indicate main effect of 'leg'
** Mixed linear model adjusted for baseline assessment, age and sex. P-value indicate main effect of 'leg'