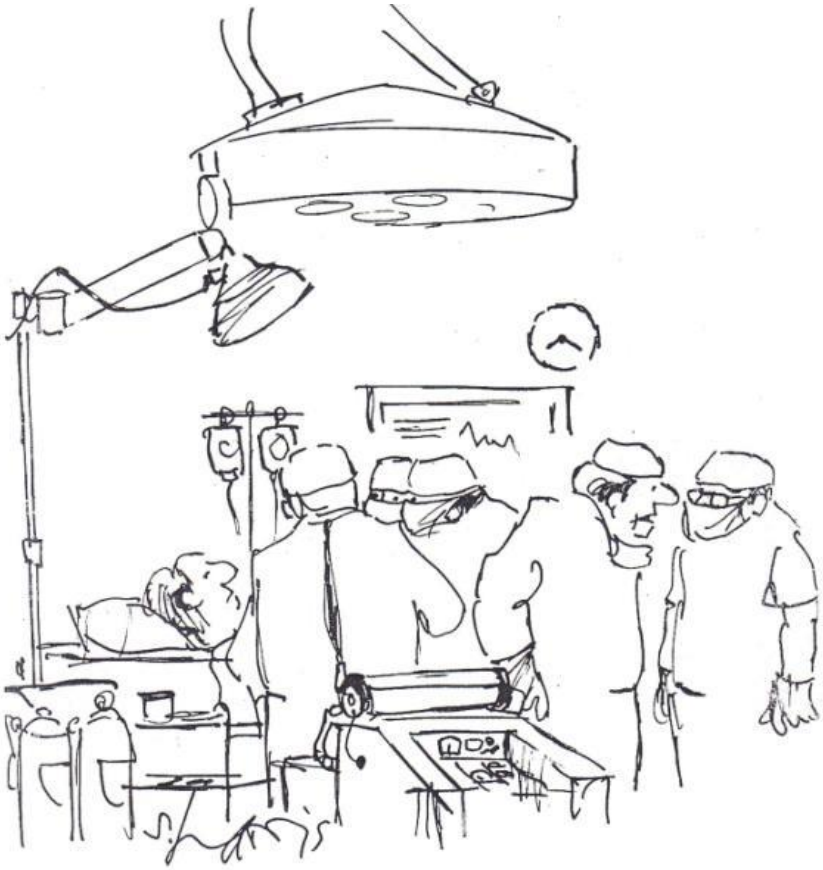
Surgery for Degenerative Meniscus Tears: Incidence, Symptoms and Placebo Treatment

Research Unit for Musculoskeletal Function and Physiotherapy

Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Denmark

Department of Orthopedics, Slagelse Medical Hospital, Region Zealand, Denmark



"WE'LL JUST MILL AROUND TILL HE'S ASLEEP, AND THEN SEND HIM BACK UP. THIS OPERATION IS ACTUALLY FOR A PLACEBO EFFECT."

Kristoffer Borbjerg Hare, MD

PhD Thesis 2015

Print: Print & Sign, SDU

Table of content

Front page: Drawing by S. Harris, reprinted with permission.

List of papers

This dissertation is based on the following papers referred to by their Roman numerals:

Paper I

Jonas B. Thorlund, Kristoffer B. Hare, L. Stefan Lohmander

Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011

Acta Orthopaedica 2014 June; 85(3): 287-92

Paper II

Kristoffer B. Hare, Jesper H. Vinther, L. Stefan Lohmander, Jonas B. Thorlund

Large regional differences in number of arthroscopic meniscal procedures at public and private hospitals in Denmark

Accepted in *BMJ Open* January 2015

Paper III

Kristoffer B. Hare, L. Stefan Lohmander, Nina Jullum Kise, May Arna Risberg, Ewa M. Roos

Self-reported knee symptoms in 199 patients with an MRI-verified meniscal tear eligible for arthroscopic partial meniscectomy: a cross sectional study.

In manuscript

Paper IV

Kristoffer B. Hare, L. Stefan Lohmander, Robin Christensen, Ewa M. Roos

Arthroscopic Partial Meniscectomy in Middle-Aged Patients with Mild or No Knee Osteoarthritis: A Protocol for a Double-Blind, Randomized Sham-Controlled Multi-Centre Trial

BMC Musculoskeletal Disorders 2013 Feb 25; 14: 71

Paper V

Kristoffer B. Hare, L. Stefan Lohmander, Ewa M. Roos

The Challenge of Recruiting patients into a placebo controlled surgical trial

Trials 2014 May 13; 15: 167

Contributions

Paper I

Study design	Jonas Bloch Thorlund
	L Stefan Lohmander
Data collection	Jonas Bloch Thorlund
	Kristoffer Borbjerg Hare
Data analysis	Jonas Bloch Thorlund
Manuscript writing	Jonas Bloch Thorlund
Manuscript revision	Jonas Bloch Thorlund
	Kristoffer Borbjerg Hare
	L Stefan Lohmander
Journal correspondence	Jonas Bloch Thorlund

Paper II

Study design	Jonas Bloch Thorlund
	L Stefan Lohmander
Data collection	Kristoffer Borbjerg Hare
	Jesper Høeg Vinther
	Jonas Bloch Thorlund
Data analysis	Kristoffer Borbjerg Hare
Manuscript writing	Kristoffer Borbjerg Hare
Manuscript revision	Kristoffer Borbjerg Hare
	Jesper Høeg Vinther
	L Stefan Lohmander
	Jonas Bloch Thorlund
Journal correspondence	Kristoffer Borbjerg Hare

Paper III

Study design	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Ewa M Roos
Data collection	Kristoffer Borbjerg Hare
	Silje Stensrud
	Nina Jullum Kise
Data analysis	Kristoffer Borbjerg Hare
Manuscript writing	Kristoffer Borbjerg Hare
Manuscript revision	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Nina Jullum Kise
	May Arna Risberg
	Ewa M Roos
Journal correspondence	Kristoffer Borbjerg Hare

Paper IV

Study design	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Ewa M Roos
Data collection	Kristoffer Borbjerg Hare
Data analysis	Kristoffer Borbjerg Hare
	Robin Christensen
Manuscript writing	Kristoffer Borbjerg Hare
Manuscript revision	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Robin Christensen
	Ewa M Roos
Journal correspondence	Kristoffer Borbjerg Hare

Paper V

Study design	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Ewa M Roos
Data collection	Kristoffer Borbjerg Hare
Data analysis	Kristoffer Borbjerg Hare
Manuscript writing	Kristoffer Borbjerg Hare
Manuscript revision	Kristoffer Borbjerg Hare
	L Stefan Lohmander
	Ewa M Roos
Journal correspondence	Kristoffer Borbjerg Hare

Abbreviations

ACL – Anterior cruciate ligament

APM – Arthroscopic partial meniscectomy

BMI – Body Mass Index

DNPR – Danish National Patient Registry

ICD - International Classification of Diseases

ITT – Intention to treat

JSW – Joint Space Width

K&L – Kellgren and Lawrence

KOOS – Knee Injury and Osteoarthritis Outcome Score

MRI – Magnetic Resonance Imaging

NCSP - Nordic Classification of Surgical Procedures

NNA – Number needed to be allocated

NNS – Number needed to be screened

OA – Osteoarthritis

PRO – Patient Reported Outcome

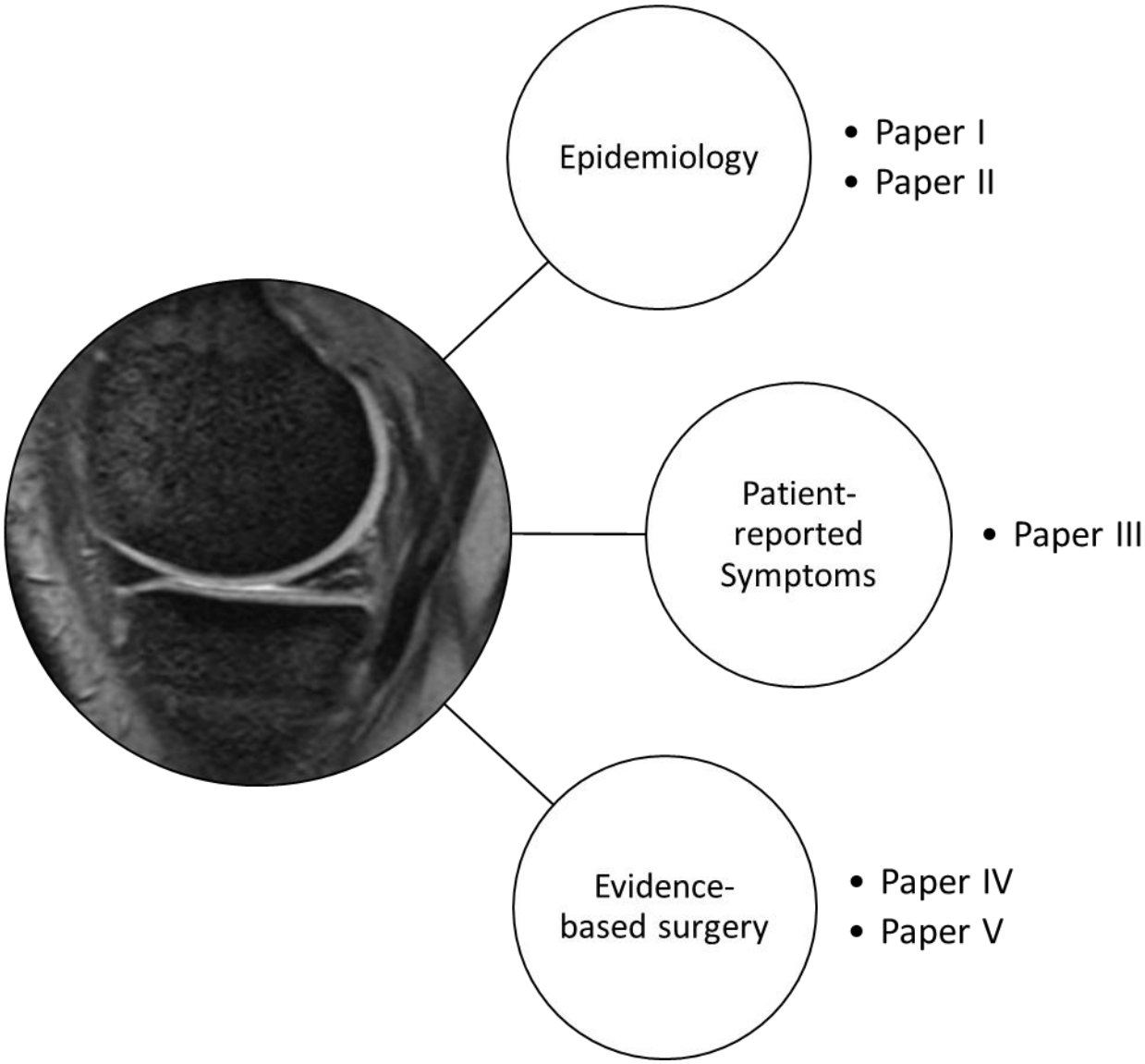
PCL – Posterior cruciate ligament

RCT – Randomized controlled trial

SLAMSHAM – **SL**agelse **A**rthroscopic **M**eniscectomy vs. **SHAM** surgery

Thesis at a glance

This thesis comprises five studies with different perspectives on arthroscopic treatment of degenerative medial meniscus tears. Papers I and II studied the incidence of arthroscopic meniscus procedures in Denmark from year 2000 to 2011. Paper III reported the frequency and severity of knee symptoms in patients deemed eligible for arthroscopic partial meniscectomy and the influence of concomitant radiographic structural disease on these symptoms. Paper IV described the protocol of a sham surgery controlled randomized controlled trial of degenerative meniscus tears, while paper V focused on the challenges of recruiting patients into a sham controlled surgical trial and investigated reasons for participation. Recruitment for the randomized sham-controlled trial was still ongoing at the time of finalizing this thesis, and the results of this trial are thus not part of this thesis.



Paper I – What is the incidence of arthroscopic procedures on the meniscus in Denmark?

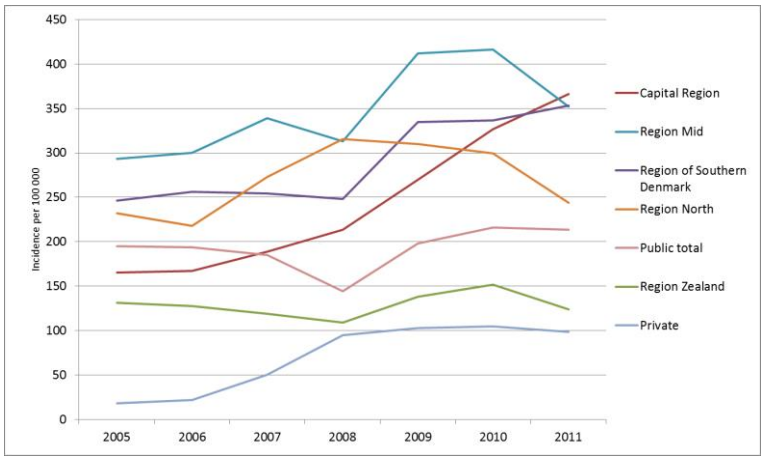
Patients: 151 228 procedures in 148 819 patients.
Method: Data extracted from Danish National Patient Registry
Conclusion: Incidence of meniscus procedures doubled in the year 2000 to 2011. Most of the procedures were performed in middle-aged and older patients and meniscus resection accounted for 92% of the procedures.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
<35 years	129 (124-133)	127 (122-131)	135 (131-140)	132 (128-137)	129 (125-134)	126 (122-131)	128 (123-132)	127 (123-132)	122 (118-127)	147 (142-152)	158 (153-163)	155 (150-160)
35-55 years	256 (248-264)	273 (265-281)	308 (300-317)	332 (323-341)	343 (334-352)	356 (347-366)	358 (349-368)	395 (385-405)	402 (392-412)	520 (509-531)	536 (524-547)	526 (515-537)
>55 years	115 (110-121)	126 (120-132)	156 (149-162)	167 (161-174)	173 (167-180)	196 (189-204)	202 (194-209)	233 (226-241)	245 (237-253)	305 (297-314)	341 (332-350)	324 (315-333)
Total	164 (161-168)	171 (167-174)	193 (189-197)	202 (198-207)	205 (201-209)	214 (210-218)	216 (212-220)	236 (232-240)	239 (235-244)	301 (297-306)	321 (316-326)	312 (308-317)

Numbers in table show incidence per 100 000 (95% confidence intervals)

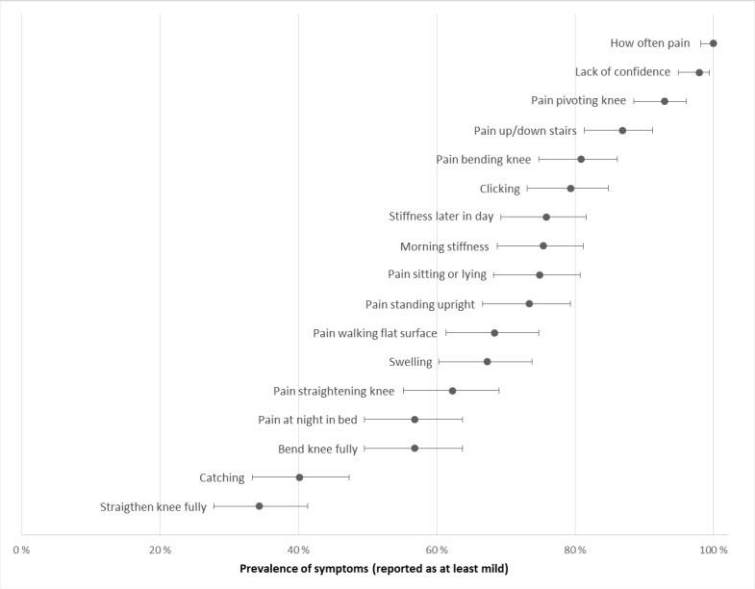
Paper II – What are the regional differences in the provision of arthroscopic procedures?

Patients: 151 228 procedures in 148 819 patients.
Method: Data extracted from Danish National Patient Registry
Conclusion: Large regional differences are apparent in the use and provision of arthroscopic meniscus procedures. Private hospital and clinics accounted for the largest increase in incidence of meniscus procedures from year 2005 to 2011.



Paper III – Which symptoms are related to a degenerative meniscus tear?

Patients: 199 patients, 41% women, mean age 48.
Method: Cross-sectional study, self-reported symptoms obtained by the use of KOOS.
Conclusion: Middle-aged patients with a degenerative medial meniscus tear report symptoms commonly associated with knee osteoarthritis. Those reporting swelling of the knee, stiffness later in day or catching were at higher risk of radiographic signs of concomitant structural disease. These findings support the hypothesis that a symptomatic degenerative meniscal tear is an early sign of knee osteoarthritis. Neither mechanical nor other symptoms can be attributed to the degenerative meniscal tear as such, but rather to the ongoing degenerative process.



Paper IV – A protocol for a placebo controlled orthopedic trial. SLagelse Arthroscopic Meniscectomy vs. SHAM surgery.

Patients: 80 patients, middle-aged with an MRI confirmed degenerative meniscus tear will be recruited.

Method: RCT, placebo surgery vs. arthroscopic partial meniscectomy, 2-year follow-up, KOOS and physical function tests.

Conclusion: The results of the SLAMSHAM study will either support continuing use of APM or indicate that the efficacy of APM is comparable to or less than placebo and should be discontinued.

Paper V – The feasibility of conducting a placebo controlled surgical RCT

Patients: 476 patients screened, 190 eligible, 40 included in the RCT.

Method: Number needed to screen and number needed to allocate were calculated. Rationale for joining the study and type of information most useful for deciding upon participation was investigated.

Conclusion: Patients were willing to participate in an orthopedic placebo controlled surgical trial. Oral information given by the surgeon to the patient and the contribution to research were important aspects to enhance patient recruitment.

Summary

The overall aim of this PhD thesis was to report the incidence of meniscus surgery and symptoms reported by middle-aged patients with degenerative meniscus tears eligible for surgery and to report the study design and process of a placebo-controlled trial evaluating the outcome of middle-aged patients undergoing arthroscopic partial meniscectomy.

In paper I, the incidence of meniscus procedures in Denmark over a 12-year period was determined. The incidence almost doubled in this time and in particular for middle-aged and older patients.

Paper II showed that a large proportion of the increase occurred in private hospitals and clinics. The regional provision of arthroscopic procedures on the meniscus varied widely in Denmark.

Paper III examined the prevalence and severity of commonly assessed self-reported knee symptoms by the use of a patient-administered questionnaire, and investigated if concomitant signs of radiographic structural disease influenced presence of self-reported knee symptoms. Middle-aged patients with a degenerative medial meniscus tear reported symptoms commonly associated with knee osteoarthritis. Patients with meniscus tears reporting swelling of the knee, stiffness later in day or catching were at higher risk of radiographic signs of concomitant structural disease.

Paper IV described the protocol for a randomized placebo controlled trial designed as a superiority study to test whether the benefit from arthroscopic partial meniscectomy in patients aged 35-55 years with knee pain and an MRI-verified medial meniscus lesion is greater after arthroscopic partial meniscectomy than following sham surgery.

In Paper V, the challenges of recruiting patients into this trial were described. The number of patients needed to be screened, and the number of patients needed to be allocated, in order to include the required number of participants into the RCT, were 11.9 and 4.8, respectively.

The large increase of arthroscopic procedures on the meniscus contrast the existing lack of evidence of added benefit of surgery compared to non-surgical interventions. Catching or locking symptoms is generally acknowledged as an indication for meniscus surgery but catching was rarely reported prior to surgery and the evidence for its relation to a meniscal tear or an added benefit from partial meniscectomy is scanty. This lack of consensus on when to perform arthroscopic meniscus surgery may partly be a reason for the large regional variation in provision of meniscus surgery. The association of catching with concomitant signs of radiographic structural disease support a proposal that a symptomatic degenerative meniscal tear is an early sign of knee osteoarthritis, and that neither mechanical nor other symptoms are specifically attributed to the degenerative meniscal tear as such, but rather to the ongoing degenerative process. Even though the randomized controlled trial is considered gold standard in therapeutic trials, it is only seldom used to evaluate even the most common orthopedic surgical procedures. There are well-known challenges in recruiting patients for surgical trials in general and adding a placebo component only adds to these challenges.

Resume

Degenerative menisk skader ses hyppigst hos midaldrende og ældre patienter. De typiske symptomer er vedvarende smerte, klikken og aflåsningstilfælde. Diagnosen stilles oftest på de kliniske fund eventuelt suppleret med en MR skanning af knæet. De kliniske test for menisk skader er dog forbundet med stor usikkerhed og halvdelen af de meniskskader man ser på en MR skanning, ses hos patienter uden symptomer fra knæet. Den typiske behandling af menisk skader er artroskopisk partiel meniskresektion. På verdensplan er det den mest hyppige ortopædkirurgiske procedure. Eksisterende studier har dog ikke fundet nogen øget effekt af dette indgreb i tillæg til træning eller sammenlignet med placebo (snyde) kirurgi.

Formålet med denne afhandling var derfor at se på forekomsten af menisk operationer i Danmark, hvilke symptomer der relaterer sig til meniskskader og rapportere fra planlægningen og rekrutteringen af et randomiseret placebo kontrolleret studie af degenerative meniskskader hos midaldrende patienter. Resultaterne fra det randomiserede studie indgår ikke i denne afhandling.

Det første studie i denne afhandling fandt en fordobling af antallet af artroskopiske menisk operationer fra år 2000 til år 2011. Primært midaldrende og ældre patienter blev opereret og 92% af operationerne var meniskresektioner.

Studie 2 fandt store regionale forskelle i forekomsten af menisk operationer og fandt at den største stigning skete i den private sygehus sektor. Mulige årsager til den store stigning kunne være indførelse af den diagnose relaterede takst for alle procedurer i 2000 og samtidig indførelse af ventetidsgarantien, der muliggjorde at patienter kunne blive opereret på et privat sygehus såfremt den offentlige sektor ikke kunne tilbyde operation inden for en måned.

Studie 3 rapporterede forekomsten og sværhedsgraden af selv-rapporterede symptomer hos patienter fundet egnede til partiel meniskresektion. Studiet fandt en forekomst af symptomer som typisk også ses hos patienter med knæ artrose og fandt at radiologiske strukturelle forandringer var forbundet med øget risiko for aflåsningstilfælde, hævelse og stivhed i leddet.

Det fjerde studie beskrev designet af et randomiseret placebo kontrolleret studie af midaldrende patienter med knæsmerter og en MR verificeret degenerativ menisk læsion. Studiet var designet til at vise om artroskopisk menisk resektion var bedre end en placebo operation målt på smerte og funktion.

Det femte studie rapporterede udfordringerne ved at rekruttere til et placebo kontrolleret kirurgisk studie. Antallet af patienter der skulle screenes for at inkludere en patient var 11,9 og antallet af egnede patienter der skulle findes for at inkludere én var 4,8.

Den store stigning i antallet af artroskopiske menisk resektioner i Danmark står i stor kontrast til den stigende evidens som ikke har fundet øget effekt af kirurgi sammenlignet med ikke-kirurgiske interventioner. Store regionale forskelle i anvendeligheden af menisk resektioner tyder på manglende konsensus om indikationerne for kirurgi. Mekaniske symptomer er ofte forbundet med menisk læsioner men aflåsningstilfælde var sjældent rapporteret forud for kirurgi og der er mangelfuld evidens for at knytte aflåsningstilfælde til menisk læsioner. Associationen mellem aflåsningstilfælde og radiologiske strukturelle forandringer tyder på at en symptomatisk degenerativ menisk læsion er et tidligt tegn på knæ artrose og at

hverken mekaniske eller andre symptomer er forbundet med selve menisk læsionen men mere den igangværende degenerative proces i hele knæet. Randomiserede kontrollerede studier regnes for højeste standard inden for terapeutiske studier men er trods dette kun sjældent anvendt for selv de mest hyppige ortopædkirurgiske interventioner. Velkendte udfordringer, såsom patient rekruttering og etiske overvejelser kan være en hindring.

Introduction

Degenerative meniscus tears are common in the population [1] and a daily encounter for orthopedic surgeons in the clinic. Indeed, arthroscopic partial meniscectomy (APM), is the most frequently performed orthopedic procedure, carried out on more than half a million patients annually in the USA alone [2, 3]. However, clinical challenges remain in both diagnosing and optimal treatment of a symptomatic degenerative meniscus tear. Since the discovery of the meniscus as an important functional structure and not only a functionless remnant [4] surgical treatment shifted from total meniscectomy to arthroscopic partial meniscectomy. APM was shown to be superior to total meniscectomy and open technique in terms of short-term recovery and length of hospital stay [5, 6]. Nevertheless, despite more than 30 years of experience with arthroscopic treatment of meniscus tears, we have only recently begun to understand the role of a degenerative meniscus tear and the implications of arthroscopic surgery. No consensus exists on when APM is indicated [7] and uncertainty remains on the added benefit, if any, of APM compared to non-surgical interventions [8-14]. These circumstances are reflected in the provision of APM, which varies widely within regions of a single country [15, 16].

The role of the meniscus

The meniscus plays an important role in knee function and in preservation of the knee joint. The primary role of the meniscus is to distribute joint load and thereby decrease the load on the articular cartilage. Secondly the meniscus contributes to shock absorption, stability, and proprioception of the knee joint [17].

Anatomy

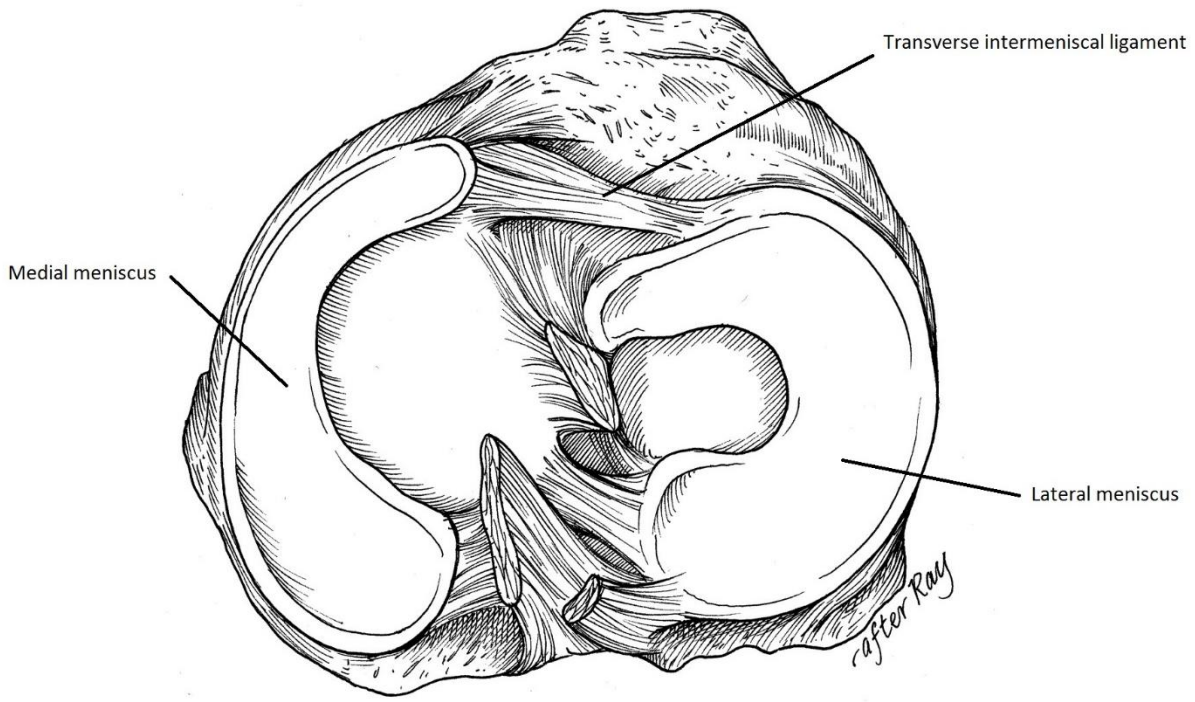


Figure 1 Anatomy of the menisci viewed from above (adapted image reprinted with permission from Pagnani MJ, Warren RF, Arnoczky SP, Wickiewics T. The lower Extremity and Spine in Sports Medicine. 1995, p 581-614, © Mosby).

The menisci are C-shaped structures with anterior and posterior horns. In cross-section, the meniscus is wedge shaped with the outer rim thick and attached to the joint capsule while the inner edge is thin and unattached. The medial meniscus is larger than the lateral meniscus and its posterior horn is larger than the anterior. The medial meniscus in inserted posterior in tibia just anterior to the insertion site of the posterior cruciate ligament (PCL). The anterior horn is inserted in the tibia anterior to the anterior cruciate ligament (ACL). In addition, the peripheral border of the medial meniscus is attached to the joint capsule and the medial collateral ligament (MCL) making the medial meniscus less mobile than the lateral meniscus [18, 19].

The meniscus receives blood supply from branches of the popliteal artery (the medial, lateral inferior and middle geniculate arteries). Only 10-30% of the periphery of the meniscus is vascularized [20], the red zone, while the inner part of the meniscus is not vascularized (the white zone). This has important influence on potential meniscus healing. The meniscus receives innervation from the recurrent peroneal branch of the common peroneal nerve [21, 22]. The nerve fibers follow the blood supply and are primarily present in the peripheral vascular zone. Mechanoreceptors have been located in the anterior and posterior horn of the meniscus and are believed to play a proprioceptive role [17].

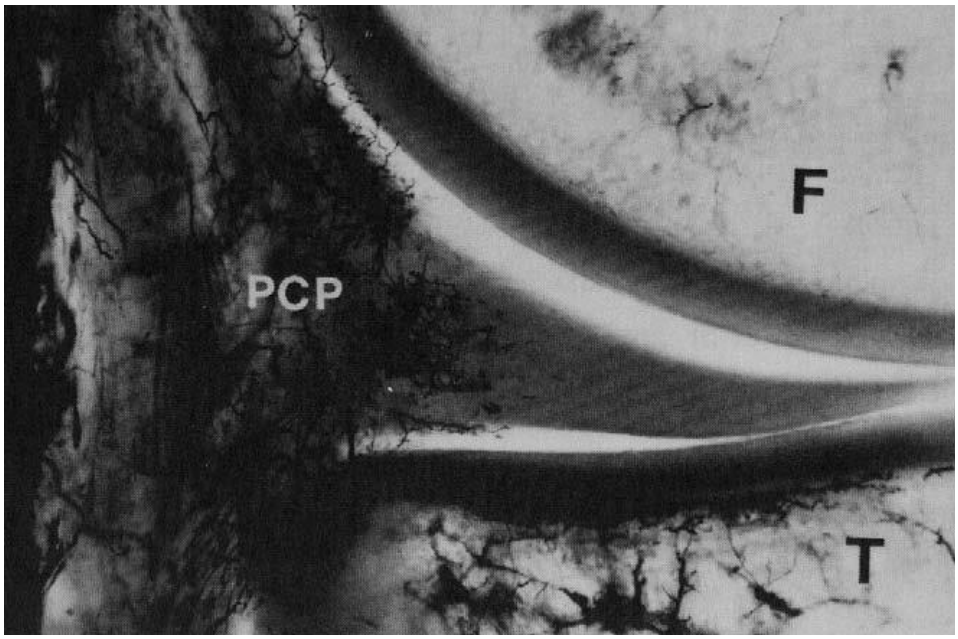


Figure 2 Frontal section of medial compartment. Peripheral capillary plexus (PCP) can be observed (reprinted with permission from Arnoczky SP, Warren RF. Am J Sports Med 1982, 10, 90-95).

The meniscus is composed mainly of water (77%) and collagen (22%) with interposed cells. In addition, proteoglycans, glycoproteins and elastin are present. The proportions vary according to age, injury and presence of a pathological condition [23]. Type I collagen is predominant in the red zone while both collagen type II and I are present in the white zone outside the vascularized peripheral of the meniscus [17, 24]. The collagens in the peripheral red zone are arranged circumferentially with some type I fibers woven between the circumferential fibers to provide structural integrity. This is ideal for dealing with axial forces since compression will result in circumferential stresses. In the white zone, the collagens are cross-linked, which helps transferring vertical compressive forces.

Function

The main role of the meniscus is load transmission from the concave femur condyles to the relatively flat tibia condyles. In the extended knee, 40-60% of the load is transmitted to the meniscus. In flexion, this rises up to 90%. It is believed that the menisci contribute to shock absorption in the knee due to their viscoelastic properties and a 20% reduction of shock absorption have been shown in knees without a meniscus [25]. The meniscus also contributes to anterior stability of the knee. The firm attachment of the medial meniscus to tibia has been demonstrated to enhance joint stability in studies of ACL deficient knees with or without medial meniscectomy [26, 27].

Meniscus tears

Definition

Meniscal tears are by health-care professionals and laypersons often associated with traumatic sports injuries in young active individuals [28]. In Denmark the incidence of meniscus tears was reported about 70 per 100 000 persons in emergency departments [29]. Traumatic tears are typically spit vertically in line with the orientation of the circumferentially oriented collagen fiber, resulting in a longitudinal tear.

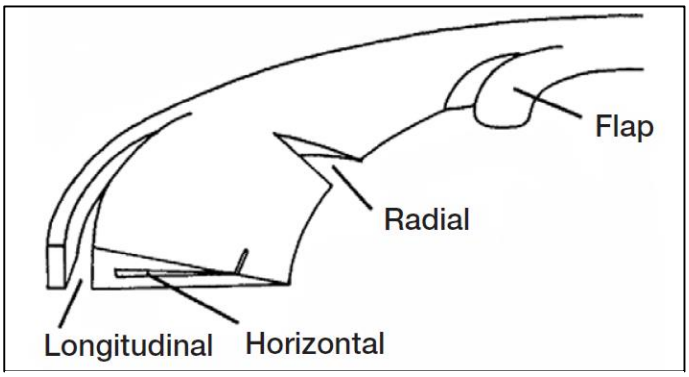


Figure 3 Types of meniscus tears (reprinted with permission from Harald R, Thesis 1994 Exercise, knee injury and osteoarthrosis, 21).

In contrast to the traumatic tear in younger patients, the degenerative meniscus tears are typically seen in middle-aged and older patients as horizontal lesions or flap tears of the body or posterior horn and most often of the medial meniscus. The prevalence of degenerative meniscus tears range from 19% in women aged 50-59 years to over 50% in men aged 70-90 years. Over 60% of meniscus tears are found in subjects without knee pain or other symptoms [1]. In patients with concomitant symptomatic knee OA, the prevalence of meniscus pathology is even higher, about 70-90% [30, 31].

Risk factors

Risk factors for meniscus tears are often thought of as sports injuries with some kind of trauma involved. For traumatic tears, this is also true. However, for degenerative meniscus tear, a high-energy trauma is often not involved. Indeed, the strongest evidence for risk of meniscus tear is associated with age, work-related kneeling or squatting and walking up or down stairs. There is also a medium association with increased Body Mass Index (BMI) above 25, walking, standing and lifting heavy objects. There is no evidence for associated risk with lifestyle habits such as smoking or alcohol consumption [32].

Diagnosis

The diagnostic criteria of a degenerative medial meniscus tear are not consistently defined. Often the clinician relies on patient history and clinical test to identify a suspected symptomatic tear. Symptoms commonly considered related to meniscus injury include knee pain, giving way and mechanical symptoms like clicking, locking or catching, and there is some evidence for their validity in identifying symptomatic meniscus tears when clinical history is ascertained by the clinician [33-35]. Clinical tests however have not proven to be very accurate and repeat studies suggest that no single test can definitively diagnose a

symptomatic meniscus tear [36-40]. Therefore, Magnetic Resonance Imaging (MRI) has been used as a diagnostic tool and has been shown to reliably identify meniscus tears in symptomatic patients [41]. However, since MRI also detects asymptomatic meniscus tears in the population [1], the final diagnosis of a clinically relevant meniscal tear often relies on multiple sources of information.

Surgical treatment of degenerative meniscus tears

Arthroscopic partial meniscectomy has for decades been the preferred treatment of degenerative meniscus tears in the painful knee. The procedure consists of resection of the damaged part of the meniscus and trimming of the remaining meniscus. The seemingly positive effect of this treatment was observed in numerous observational studies, which all concluded a good outcome for patients with degenerative meniscus tears after this procedure [42-46].

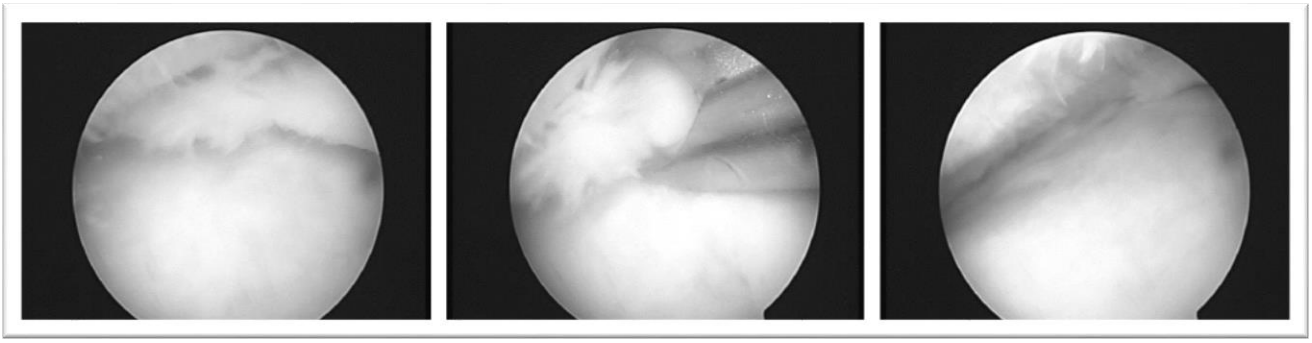


Figure 4 Pictures showing before, during and after an arthroscopic partial meniscectomy (reprinted with permission from Rønne, K).

However, in 2002, the first placebo controlled study of arthroscopy revealed a surprisingly large placebo effect of arthroscopy in patients with knee OA, and no difference in pain relief compared to debridement of the knee including resection of the meniscus [47]. Six years later Kirkley et al. found that patients with knee OA had equal benefit from exercise therapy alone compared to arthroscopic debridement and exercise [48].

In 2007, Herrlin found no added benefit from APM and exercise therapy compared to exercise alone and confirmed these findings in a long-term follow-up [10, 12]. In 2013, two studies comparing APM and exercise therapy with exercise therapy alone again confirmed these findings [9, 49]. The perhaps most convincing study compared APM to a diagnostic arthroscopy or placebo procedure, and found no difference in several outcome scores including patient satisfaction. More than 90% in both groups were willing to repeat the procedure. A recent meta-analysis, concluded there was no added benefit to arthroscopic meniscus debridement for degenerative meniscus tears in comparison with non-operative or sham treatment options for middle-aged patients with mild or no concomitant knee osteoarthritis [14]. Only one recent study showed an added benefit of APM over a non-surgical intervention in patients with degenerative meniscus tear [13]. Patients in the control group of that study received a non-supervised/home-based exercise program after instructions from a physiotherapist. However, these recent findings must be considered along with the previous RCT's contradicting these results. The overall impression of the existing evidence remain that APM fail to show superiority over non-surgical interventions. If further studies favors surgical treatment, the conclusion should be revised through updated systematic reviews and meta-analysis.

Eligibility for surgery

Since no consensus exists on the exact diagnosis of a symptomatic degenerative medial meniscus tears, a similar lack of consensus exists on when to perform APM. One, almost universally agreed, indication for APM is however the experience of catching or locking symptoms in the presence of an MRI-verified meniscus tear [7]. However, studies have shown that even patients with catching symptoms may get better without surgery [11] and in a recent study of APM, patients with catching or locking symptoms did not gain more from APM than those without [13]. Therefore, even though catching or locking is generally acknowledged as an indication for surgery, the evidence therefore is scanty.

On the other hand, some clinicians are reluctant to perform APM in patients with concomitant radiographic knee OA and studies suggest that co-existing radiographic knee OA is a negative predictor for outcome after APM [7, 50]. Presence of a degenerative meniscus tear can be an early sign of knee OA and knee OA can be present even in the absence of radiographic changes [28]. If so, coexisting knee OA may be the primary cause of knee pain and symptoms, even in the presence of a meniscus tear shown on MRI and no radiographic knee OA in a symptomatic patient [28].

Consequences of APM

The surgical resection of the meniscus leads to increased joint cartilage contact stress through altered load transmission, decreased shock absorption, and decreased joint stability [51, 52]. In patients who undergo either total or partial meniscectomy, 50% on average develop knee OA within 10-20 years [53] and amount of removed meniscus is the most important factor for the development of knee OA [54]. In the elderly population in general, and in patients with radiographic knee OA but no previous surgery, there is a higher incidence of MRI-verified concomitant meniscus injury compared to controls [55]. It remains unclear though, whether meniscectomy increases the risk of knee OA *per se*, compared to non-surgical treatment of a meniscus injury.

Arthroscopic surgery of the knee is generally considered low-risk surgery and has been reported to be associated with a 2–3% frequency of adverse events, including deep venous thrombosis, infections, surgical complications, cardiovascular events, pulmonary embolism, and death within 3 months [56-59]. Even though this rate of complications is low, it represents a large burden for the individual patient and socioeconomic costs [60]. In addition, these complications should be considered along with the low evidence of added benefit of many of these procedures.

Evidence based orthopedic surgery

There is a long tradition to perform randomized controlled trials when evaluating healthcare interventions. The randomization of treatment and blinding of group allocation to the investigator and participants allows for reduction of bias. This design is considered gold standard in therapeutic trials but is only seldom used for even the most common orthopedic surgical procedures [61].

Recruitment challenges

Well-known challenges in recruiting patients for surgical trials in general [62, 63] may in part be reason for a reluctance to perform surgical RCT's. Often both surgeons and patients have a strong preference for one therapy over another and patients may refuse to participate in a trial. Even for diseases or conditions with a high prevalence only a subgroup of the population may be eligible for actual surgery. Adding a placebo component to a surgical trial only adds to the challenge of recruiting patients and even the surgeon may be

reluctant to perform an actual placebo procedure. Ethical concerns are often expressed as an argument against placebo controlled surgical RCT's [64, 65], often claiming it is unethical to 'harm' the patients with a surgical intervention without any chance of genuine therapeutic effect.

The placebo effect

The word placebo means 'I please' and was originally used to imply a deception, or fraud of patients. With the introduction of RCT's the meaning of the word placebo has changed to the response to a dummy treatment used as the 'control' for the real treatment. The inert placebo effect have been effectively demonstrated in a number of trials [66-68] and even demonstrated in a variety of surgical trials [8, 47, 69-71]. The term 'placebo response' can be misleading since a dummy treatment with no active therapeutic effect cannot do anything. However, if there is no real effect, then what causes the placebo response? The placebo effect has been described to consist of many components. There is a psychosocial context, such as faith in treatment, expectations, learning and neurophysiologic factors. The clinician contributes with enthusiasm, empathy, security and also their faith in the treatment [72]. The delivery of the treatment also influences the placebo effect. It is known that the placebo effect rises when the delivery is more invasive In knee OA patients, intra-articular injection of saline has a stronger placebo effect than a placebo pill and surgery has a stronger effect than injection [73]. In addition, the placebo response does not necessarily refer to the genuine psychosocial response to the stimulation of a dummy treatment alone but also includes natural course of disease, fluctuation of symptoms, regression to the mean or response bias with respect to patient reported outcomes [72].

Aims

General aim

The overall aim of this PhD thesis was to report the incidence of meniscus surgery and symptoms reported by middle-aged patients with degenerative meniscus tears eligible for surgery and to report the study design and process of a placebo-controlled trial evaluating the outcome of middle-aged patients undergoing arthroscopic partial meniscectomy.

Specific aims

The specific aims of this thesis were:

- To examine the number of meniscal procedures performed in the years between 2000 and 2011 in Denmark, as well as the age and gender distribution and the registered diagnosis of the patients undergoing these procedures using data from The Danish National Patient Register.

- To elucidate the use of arthroscopy for meniscal tears in Denmark, by investigating the number of meniscal procedures performed in the public and private sector, and regional differences in the use of these procedures.

- To determine the prevalence and severity of commonly assessed self-reported knee symptoms by the use of a patient-administered questionnaire and investigate if concomitant signs of early radiographic knee OA influenced presence of these symptoms.

- To describe the protocol for a randomized placebo controlled trial designed to test whether the benefit from arthroscopic partial meniscectomy in patients aged 35-55 years with knee pain and an MRI-verified medial meniscus lesion, is greater after arthroscopic partial meniscectomy than following sham surgery.

- To describe the challenges of recruiting patients into an ongoing multi-center RCT comparing APM to a placebo surgery of degenerative meniscus tears in a younger age group, 35-55 years of age at an earlier stage of disease by
    - Providing the number of patients needed to be screened (NNS), and the number of patients needed to be allocated (NNA), in order to include the required number of participants into the RCT.
    - Identifying reasons associated with participation in a placebo controlled randomized surgical trial by asking why patients were willing to participate and which type of information was most useful for deciding upon participation.

Methods

Subjects presented in this thesis were either part of the registry study (paper I and II) or patients allocated through the recruitment process of the SLAMSHAM study (paper III-V). In addition, we included subjects from, the OMEX study (paper III).

In paper I-II, data extracted from the Danish National Patient Registry (DNPR) was approved by Statens Serum Institut (study ID: FSEID 00000526), which is the Danish authority responsible for the DNPR. In addition, the study was approved by the Danish Data Protection Agency (study ID: 2013-41-1792), which must approve all extractions of personal data for research purposes from the DNPR. As the data is only register-based the studies can be conducted without permission from the Ethics Committee according to Danish legislation (Committee Act § 1, paragraph 1).

The SLAMSHAM study is approved by the Research Ethics Committee of Region Zealand, Denmark (study ID: SJ-183), is consistent with the Declaration of Helsinki and registered on ClinicalTrials.gov (trial registration: NCT01264991).

Patients

Paper I and II

Data was extracted from the DNPR. The DNPR registers all patient contacts with hospitals (public and private) in Denmark [74]. Administrative data include unique person identification number given to all residents in Denmark (Central Person Register - CPR-number [75]), hospital identification, date and time of activity, patient municipality, etc. Clinical data include types of surgical procedures (Nordic Classification of Surgical Procedures (NCSP)) and diagnoses (International Classification of Diseases (ICD-10)). Data was retrieved on all patients who underwent arthroscopic meniscus surgery (KNGD and all sub codes) either as a primary procedure or as part of other surgery in the years 2000 to 2011 (including both years). Data was extracted on age and sex together with hospital identification code for each contact, which enables linkage of performed procedures to specific public and private hospitals/clinics as well as geographic location. For regional differences, data was obtained from 2005 to 2011 since the Regions in Denmark were first established in 2005 in a merger of different municipalities and counties.

Denmark is divided in five regions: The Capital Region, Region Zealand, Region of Southern Denmark, Region Mid and Region North. Information on numbers of registered inhabitants of all ages in each region, per January 1 for each year in the period from 2005 to 2012 was retrieved from Danish Statistics (www.statistikbanken.dk - accessed March 13). Mid-year population was estimated from numbers at the beginning and end of each year. Yearly incidence rates per 100 000 inhabitants (all ages) were calculated with 95 % confidence intervals (95 % CI) for public and private procedures for each region.

Paper	Patients	Women, %	Mean age (95 % CI)	Type of study
I & II	148 819	40	45 (45-45)	Registry
III	199	41	48 (47-49)	Cross-sectional
V	40	53	46 (44-47)	Feasibility

Table 1 Patient characteristic for all patients included in the thesis and study design

Paper III, IV and V

Eligibility criteria for the SLAMSHAM study (paper III-V) were patients between 35 and 55 years old with an MRI verified degenerative medial meniscus tears, at least 2 months duration of knee pain and no previous significant trauma, found eligible for arthroscopic partial meniscectomy. Only patients with no or mild knee osteoarthritis (OA), Kellgren and Lawrence grade 0-2 [76, 77] were included. Eligibility for surgery was based on clinical examination by an orthopedic surgeon and the presence of a degenerative meniscus tear on MRI. An increased intra-meniscus signal (often a linear signal within the meniscus) was regarded as a meniscus tear when it communicated with the inferior or superior margin of the meniscus on at least two consecutive slices from the MRI investigation.

Patients were excluded if in need of acute surgery, e.g. locking knees or high-energy trauma. Patients with grade 3 or 4 knee OA on the Kellgren & Lawrence classification [76, 77] or knee surgery within the previous 2 years was also excluded. Patients had to be able to speak Danish and be free of any drug or alcohol abuse. In addition, patients with thrombophilia were excluded to prevent a high risk of deep venous thrombosis. The patients were recruited through outpatient departments of the orthopedic clinics in Region Zealand on referral from general practitioners.

In paper III we used a cross-sectional design and included baseline data from the SLAMSHAM study and the OMEX study as well, comparing arthroscopic partial meniscectomy with exercise therapy (ClinicalTrials.gov Identifier: NCT01002794) [78-80]. In- and exclusion criteria in the OMEX study were similar except for age criteria which was 35-65 years.

Inclusion criteria
1. Knee pain > 2 months without significant trauma 2. MRI confirmed medial meniscus lesion 3. Age 35-55 4. Eligible for outpatient surgery
Exclusion criteria
1. Need for acute surgery, i.e. locking knees, high energy trauma 2. Symptoms from other musculoskeletal disorder overriding symptoms of the knee 3. Grade 3 or 4 knee OA on the Kellgren- 4. Lawrence classification 5. Knee surgery within the last 2 years 6. BMI > 35 7. Ischemic heart disease 8. Diabetic late complications 9. Thrombophilia 10. Pregnancy 11. Unable to speak Danish 12. Drug or alcohol abuse

Table 2 In- and exclusion criteria's for the SLAMSHAM study

Study size

In the SLAMSHAM study (paper IV) the sample-size calculation was based on the assumed superiority of the arthroscopic procedures over the sham procedure. For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05, assuming a common standard deviation (SD) of 15 in the $KOOS_5$ score, a sample size estimation of the ITT population indicated that 36 individuals per group would be required to obtain a power of at least 80% to detect a minimal important change (MIC) of 10 $KOOS_5$ score units. The MIC of 10 points and SD of 15 is based on findings from similar patient groups and interventions [81]. Following these estimations, it was decided to include 80 individuals in total (40 patients in each group), allowing for a 10% drop-out rate.

In paper III patients were recruited through outpatient orthopedic clinics in Denmark or Norway between 2009 and 2013. In the OMEX study the sample size for the RCT determined the current study sample (n=140). In the SLAMSHAM study, recruitment is still ongoing and study sample was determined by patients

included in the RCT (n=40) and by patients meeting all the inclusion criteria's but declined participation and were enrolled in a parallel cohort study (n=19).

The SLAMSHAM study

Design

SLAMSHAM is an abbreviation for **SL**agelse **A**rthroscopic **M**eniscectomy vs. **SHAM** surgery study. The study was designed as a prospective double-blind randomized sham-controlled, multi-centre trial (RCT). Patients was randomly allocated to receive either an APM or sham (i.e. placebo) procedure. The study was designed according to current international standards and will be reported using the recommendations in the CONSORT statement [82].

Eligible patients were screened using standardized fixed flexion radiography of both knees, to assess the degree of radiographic knee OA. If no, or at most mild, knee OA on radiographs (Kellgren & Lawrence grades 0-2) was present, information about was given. They were also handed a Patient-Reported Outcomes (PRO) questionnaire to fill out at home to minimize bias. At the second contact, the patients received an MRI scan of the affected knee and performed tests of physical function. Thereafter, the relevant researcher and the patient were informed of the MRI findings. If the MRI confirmed a medial meniscus lesion, the patient was invited to participate in the study. Patients not consenting to randomization was followed with consecutive PRO evaluation at the same time points as those included in the RCT as an observational cohort. At 3 months, patients would have a clinical examination, fill out PRO questionnaires, and perform objective tests of muscle strength and physical function. At 2 years, follow-up took place under the same conditions. At 5 years, all patients will have radiography of their knees to assess possible onset or progress of knee OA from baseline. The flowchart provides a visual description of the study (**figure 5**).

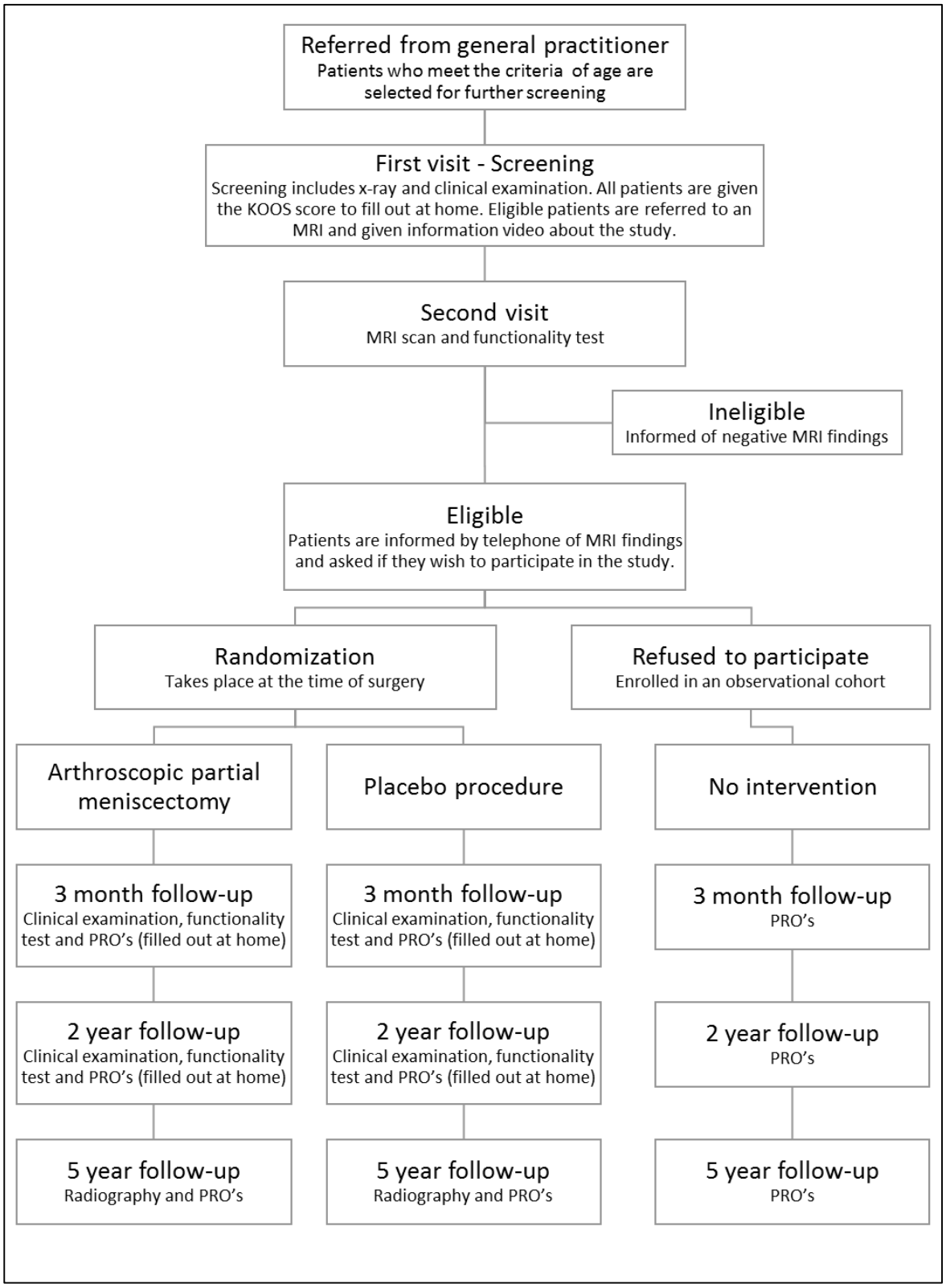


Figure 5 Flowchart of the SLAMSHAM study

Screening strategies

Patients referred from general practitioners were screened for eligibility by the principal investigator, an orthopedic surgeon in residency. If eligible, oral and written information were given about the study including a 12-minute DVD to view at home. A few days later, the patients were contacted by telephone and provided temporary consent by phone, and if willing to participate they were referred for MRI to confirm a meniscus lesion. If MRI confirmed a medial meniscus lesion the patient provided written consent, was included in the study and signed up for surgery if still willing to participate. The strategy of asking patients to participate before performing MRI was chosen since MRI is not routinely performed before arthroscopy in Denmark.

Patient information

Patients eligible for MRI all received the same oral and written information. The oral information was given by the principal investigator in a standardized way. Patients were informed of the nature of a degenerative meniscus lesion, of the treatment options and hereunder surgery. They were informed about the lack of evidence for effects of meniscus surgery in older age groups. Then they were informed of the lack of trials in their age group, the need for a study, the general concept of the placebo effect and the design of the current study, including information that placebo surgery would mean that no intervention on their meniscus tear would be performed.

The written information was identical to the oral information apart from formal information about study origin, study investigators, information on possible adverse events (most common infection and deep venous thrombosis) and other treatment modalities (i.e. exercise).

A 12-minute DVD was given to all eligible patients prior to MRI to further ensure uniform information to all patients. The video described the background for the study, the amount of involvement for participating and showed interviews of three different orthopedic surgeons with extensive experience within knee surgery giving their view on the condition and arthroscopic meniscus surgery.

Outcomes

KOOS score – paper III and IV

The primary outcome at 2 years follow-up will be $KOOS_5$, a composite score derived from the *Knee injury and Osteoarthritis Outcome Score* (KOOS) [81, 83]. The KOOS is a self-reported questionnaire comprising five subscales: pain, other symptoms, activities in daily living (ADL), function in sport and recreation, and knee-related quality of life (QOL). The previous week is taken into consideration when patients are answering the questions. Standardized answer options are given (5 boxes on a Likert scale) and each question gets a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

Subsequently, $KOOS_5$ is calculated as a mean of the 5 subscale scores [$KOOS_{pain}$ + $KOOS_{symptoms}$ + $KOOS_{ADL}$ + $KOOS_{sport\&rec}$+ $KOOS_{QOL}$] / 5.

In paper III for each individual item, presence of a symptom was defined as reporting at least mild symptoms (ticking the second out of five Likert boxes representing no, mild, moderate, severe or extreme symptoms, or equivalent).

Generic patient reported outcomes – paper IV

Scores on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36)[84, 85], which reflect the health-related quality of life (SF-36 Health Survey) – Acute version (1 week re-call period) will be used as a generic measure of patient health status at 3 and 24 months. The SF-36 is comprised of 8 single subscale scores associated with physical and mental health.

The Euroqol 5 Dimension (EQ-5D) health score will be evaluated at baseline and at 3 and 24 months as a generic measure for economic appraisal [86, 87]. EQ-5D consists of two pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems.

K&L – paper III and IV

To evaluate progression of knee OA, a fixed-flexion radiography procedure, with use of SynaFlexer [88], will be performed at baseline and after 5 years. This provides radiography at the exact same position and has been validated in determining joint space width (JSW) in knee osteoarthritis [89]. A single reader will score all the study films from baseline and 5-year follow-up and will be blinded to all clinical and questionnaire data and the baseline x-ray result but not to the sequence of the x-rays. A score will be assigned to each x-ray based on JSW and presence of osteophytes using a standard atlas [90].

The Kellgren and Lawrence (K&L) score was used to assess structural disease severity. A preoperative posterior-anterior radiograph of both knees with a fixed-flexion radiography procedure, with use of SynaFlexer [88], was performed. This provides radiography at the exact same position and has been validated in determining joint space width (JSW) in knee osteoarthritis [89]. A K&L grade of zero would imply no structural changes, a K&L grade of 1 a minute osteophytes of doubtful clinical significance, and a K&L grade of 2 a definite osteophyte with unimpaired joint space [76]. Presence of concomitant early knee OA was defined as a K&L score of 1 or 2, a K&L score of 0 implying no radiographic signs of knee OA [91-93].

Physical function test – paper IV

Single leg hop test

The one-leg hop will be included as a measure of physical function at a level above activities of daily living [94]. The one leg hop requires leg muscle strength, knee stability and confidence in knee function [95]. Subjects will perform two practice trials and then three test trials on each leg with hands behind their back. The best of the three test trials will be used. An additional trial will be performed if the patients improve more than 10 centimeters from trial two to trial three [96].

Knee-bend test

The maximum number of knee-bends performed in 30 seconds will be included as a measure of one-legged physical function required in daily life. This test requires fast changes between concentric and eccentric work and resembles stepping down a stair and is valid and reliable in meniscectomized patients [96].

Isometric knee extensor strength

Maximum knee-extension force will be measured using a hand-held dynamometer (Powertrack Commander). Patients will sit at the end of the examination couch with hip angle at 90° and knee angle at 60°. A large Velcro strap will be attached to the examination couch and the patient's ankle will be perpendicular to the lower leg. The transducer will be placed at the front of the ankle under the Velcro strap to measure knee extension force. Patients will be instructed to contract "as forcefully as possible"

with a gradual increase in force and strong verbal encouragement will be provided during the contractions. They will perform 3 contractions separated by a 60-second pause, and the highest value will be used as the result. The reliability of the isometric muscle tests with a hand-held dynamometer has been reported to be satisfactory [97-99]. The knee extension strength will be expressed as maximal voluntary torque per kilo of body mass using the external lever-arm length and body mass of each patient.

Number needed to screen and allocate – paper V

Number Needed to Screen (NNS) and allocated (NNA) are concepts previously used and described [100-102]. The NNS was calculated by dividing the number of patients screened for eligibility with the number of patients included in the trial. Similar the NNA was calculated by dividing the number of allocated patients with the number of included patients. All patients eligible for inclusion were regarded as allocated. The NNS and NNA provides an estimate of how many patients were needed to be screened and allocated to include one patient into the trial. Multiplied with the a priori determined sample size the NNS gives an estimate of how many patients needs to be screened and the NNA an approximation of the total number of eligible patients necessary.

Statistical methods

Descriptive statistics

In paper I and II, mid-year population was estimated from numbers at the beginning and end of each year. Yearly incidence rates per 100 000 inhabitants (all ages) were calculated with 95 % confidence intervals (95 % CI).

In paper III, the prevalence of knee symptoms was given as the percentage with 95 % confidence intervals (95 % CI) of patients reporting at least mild problems. Severity was given as the median with interquartile range (IQR) severity grade (range, 0-4 (no, mild, moderate, severe or extreme)) for each of the reported symptoms.

Between group difference

In paper I, chi square test was used to assess, differences in proportions of meniscal procedures performed on men and women as well as the defined age groups in 2000 compared with 2011. A two- sided unpaired t-test, assuming equal variances was used to assess differences in mean age with 95% confidence intervals (95% CI) of individuals undergoing meniscal procedures in 2000 compared with 2011.

In paper IV, treatment groups will be examined for comparability at baseline with respect to demographic and prognostic factors. An ITT analysis based on all the randomized individuals - for the efficacy measures - will apply. Comparisons between groups of the primary end point will include all repeated measures and be analyzed with the use of a mixed effects model, with random factors for participant and center.

Clinically important or relevant difference for the $KOOS_5$ and KOOS subscales were chosen as 10/100 points. Thus, a confidence interval excluding differences greater than 10 units between groups will be interpreted as indicating the absence of a clinically meaningful difference. This means that, if the 95% Confidence Interval around the group mean difference does not include a *potential* clinical benefit of 10 KOOS points, then we will then consider the therapeutic strategies equal.

Patients in the sham group who, later during the course of the study, may have an APM procedure will, still be analyzed in the group to which they were originally allocated according to the ITT principle. Secondarily,

all analyses will be supported/interpreted in the context of the corresponding results according to the per protocol populations.

Independent associations

In paper III, we used logistic regression to evaluate the association between early radiographic knee OA and presence of a symptom while adjusting for age, gender and BMI. Odds ratio, standard errors, 95% CI and p values were given for all regression analyses.

Results

Incidence of procedures on the meniscus

We found a large increase in the use of arthroscopic procedures on the meniscus in Denmark from year 2000 to 2011 (**figure 6**). Almost all of the procedures (92%) were coded as KNGD11 (arthroscopic partial resection of the meniscus) and 7% as KNGD21 (arthroscopic reinsertion of the meniscus). The largest increase was observed in the middle-aged (age 35-55) and older (age >55) population.

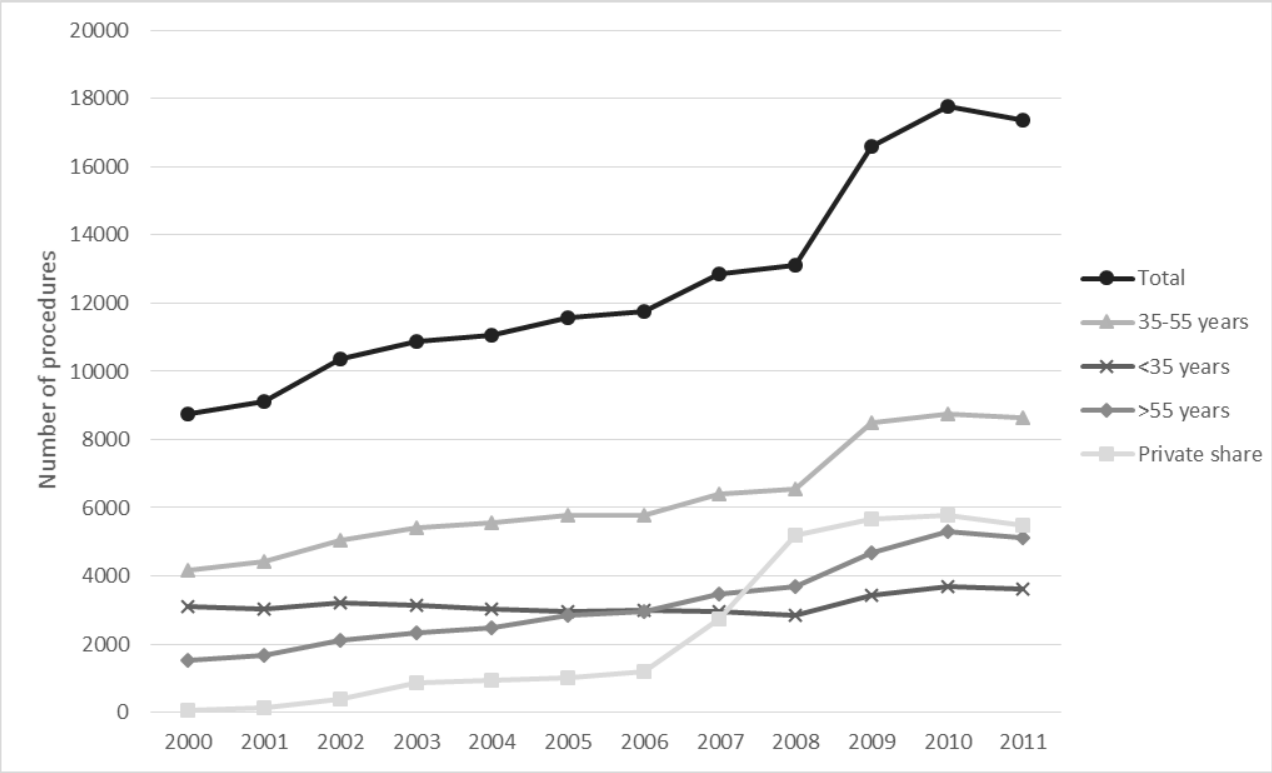


Figure 6 Number of procedures on the meniscus, divided in age group and share of procedures performed at private hospital or clinic

The proportion of procedures performed in the private sector increased from 1 % in 2000 to 32 % in 2011 and private hospitals and clinics also accounted for the largest increase in total number of procedures, rising from 65 procedures in 2000 to 5 478 in 2011.

From year, 2005 to 2011 large regional differences were present. In 2011, the total incidence rate in the Capital region was 3.0 times larger than in Region Zealand. The largest increase from year 2005 to 2011 occurred in the Capital Region while in Region Zealand and North the incidence rate remained stable.

Symptoms reported by those with a the degenerative meniscus tear

In 199 patients, the four most commonly reported symptoms were frequent knee pain, lack of confidence in knee (giving way), pain when pivoting/twisting and pain when walking up or down stairs reported by more than 80 percent of the patients. The least commonly reported symptoms were catching and difficulty straightening knee fully, reported by less than 40% of the patients. All other symptoms were reported by 50-80% of the patients.

The median frequency for knee pain was 'daily', on a scale ranging from never, monthly, weekly and daily to always. The median severity was 'moderate' on a scale from no problems, mild, moderate, and severe to extreme for lack of confidence in knee (giving way), clicking, pain when pivoting/twisting, pain when walking up or down stairs and pain when bending knee fully. The median for the two items with lowest severity, catching and difficulty straightening knee fully, was 'no problems'. For the remaining 9 items, the median severity was 'mild'.

The adjusted analysis for the association of early concomitant structural disease severity with presence of each of the 17 symptoms indicated that early concomitant structural disease (grade 1 or 2 on the K&L scale) was associated with a higher risk of self-reported swelling, catching and stiffness later in the day (**table 3**).

Symptoms		**Frequency (95% CI)**	**Severity (IQR)**	**Odds ratio (95% CI)**
P1	How often pain*	100 (98-100)	3 (2-3)	
P2	Pain when pivoting/twisting	93 (88-96)	2 (1-3)	1.4 (0.4-4.7)
P3	Pain straightening knee	62 (55-69)	1 (0-2)	1.8 (0.9-3.6)
P4	Pain bending knee	81 (78-86)	2 (1-2)	1.1 (0.5-2.5)
P5	Pain walking	68 (61-75)	1 (0-2)	1.5 (0.8-3.0)
P6	Pain going up/down stairs	87 (81-91)	2 (1-2)	1.5 (0.6-3.7)
P7	Pain at night	57 (50-64)	1 (0-2)	1.5 (0.8-2.9)
P8	Pain sitting or lying	75 (68-81)	1 (0,5-2)	1.1 (0.5-2.2)
P9	Pain standing upright	73 (67-79)	1 (0-2)	1.4 (0.7-2.8)
S1	Swelling	67 (60-74)	1 (0-2)	2.4 (1.2-4.9)
S2	Clicking	79 (73-85)	2 (1-3)	1.6 (0.7-3.5)
S3	Catching	40 (33-47)	0 (0-1)	2.3 (1.2-4.3)
S4	Straighten knee fully	34 (28-41)	0 (0-1)	1.9 (1.0-3.7)
S5	Bend the fully	57 (50-64)	1 (0-2)	1.8 (1.0-3.4)
S6	Morning stiffness	75 (69-81)	1 (1-2)	1.4 (0.7-2.9)
S7	Stiffness later in day	76 (69-82)	1 (1-2)	2.3 (1.1-5.0)
Q3	Giving way	98 (95-99)	2 (2-3)	0.5 (0.1-4.1)

*Since pain was present for all patients no logistic regression analysis was carried out.

Table 3 Frequency, severity and odds ratio for association between radiographic structural disease (K&L≥1) and knee symptoms

Feasibility of a placebo controlled surgical trial (paper IV-V)

Since start of the SLAMSHAM study, 476 patients with a suspicion of medial meniscus injury referred from their general practitioner entered the screening group. 190 patients fulfilled the inclusion and exclusion criteria and were thus eligible for MRI. However, of these 102 patients declined to participate in the study. More specifically, 77 did not wish to participate after reviewing the patient information. The reasons being; a) not wanting placebo surgery (38%), b) the risk of undergoing a secondary operation if allocated to the placebo group (21%), and c) not wanting surgery at all (19%). Five percent did not want to participate in any scientific study and 17 % had other reasons, mostly work-related. 25 patients declined participation already before reviewing the patient information and their reasons for declining participation were not collected. In addition, 46 were excluded after no visible meniscus tear was seen on MRI. Finally, 40 patients were included in the RCT (**Figure 7**). To include one patient into the RCT, 11.9 individuals with suspicion of meniscus lesion needed to be screened. Similarly, the NNA was 4.8 individuals eligible for inclusion (prior to MRI), to include one patient in the RCT.

Of the forty included patients the most common reason (90%, 80-100, 95% CI) for participating was the contribution to research compared to other reasons (10%, 10-20). 69% (54-84) of participating patients considered the oral information from the including orthopedic surgeon as most important compared to the written information and DVD (31%, 16-46).

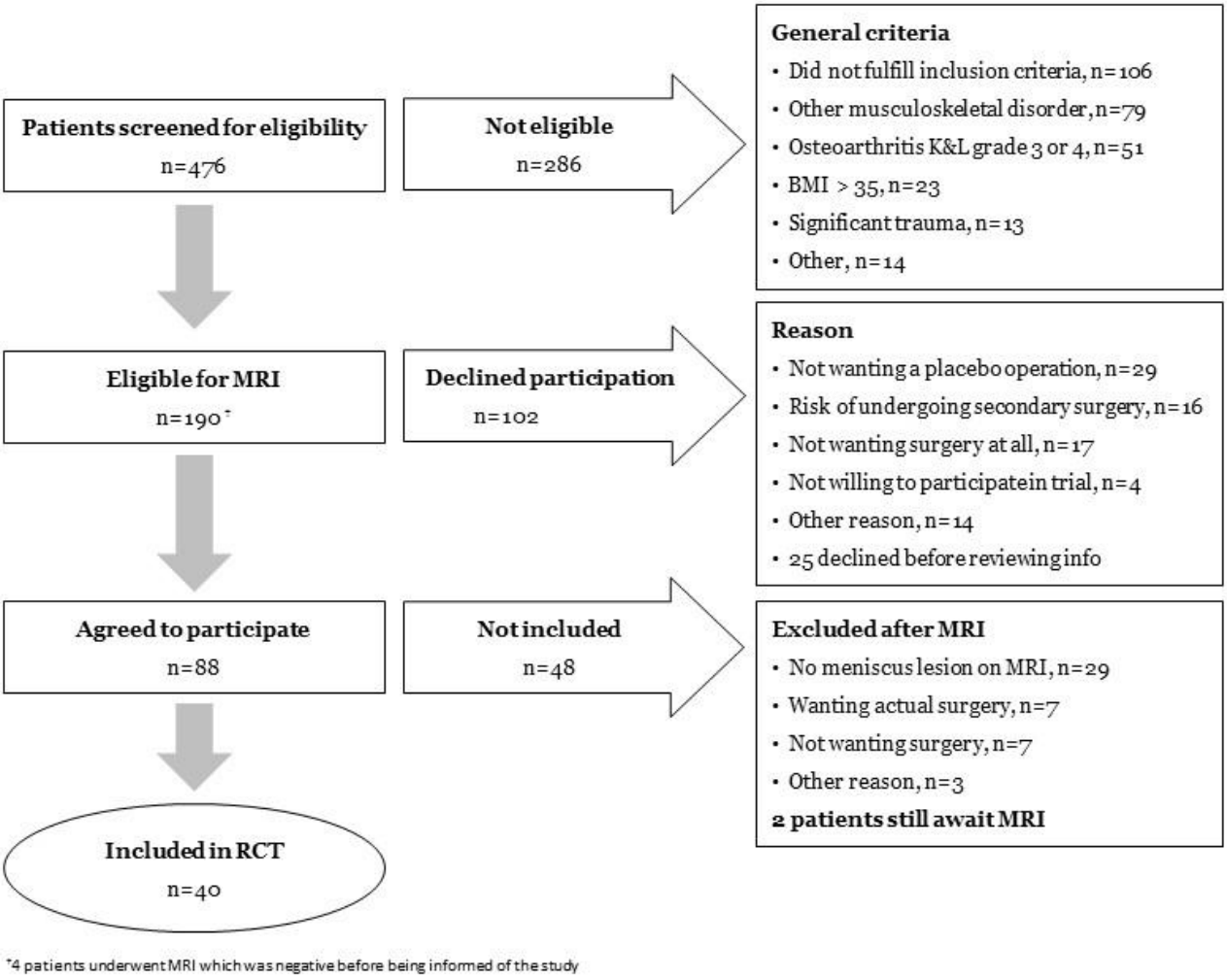


Figure 7 Flowchart of the recruitment process in the SLAMSHAM study

Discussion

Main findings

The main findings of this thesis were that the incidence of arthroscopic procedures on the meniscus doubled between 2000 and 2011 in Denmark. The proportion of procedures performed in the private sector increased from 1% to 32% over the 12-year period. In the same time period the incidence of meniscus procedures performed in the public sector increased by 31%. A large variation existed in the provision of these procedures between the 5 regions of Denmark between 2005 and 2011. In 2011 the incidence of procedures on the meniscus was 3 times higher in the Capital Region than in Region Zealand. Furthermore, in a cohort of 199 patients deemed eligible for APM, catching or locking, the symptom most commonly used as an indication for meniscus surgery, was more frequent reported in those with than in those without concomitant radiographic structural disease. Finally, 46% of eligible patients were willing to participate in a placebo-controlled arthroscopy study. However 11.9 patients needed to be screened and 4.8 eligible patients needed to be allocated in order to include one patient into the study.

Strengths and limitations

Paper I and II

A potential limitation to papers I and II is the validity of the data source, the DNPR. The DNPR is a unique registration of all hospital contacts and performed procedures in Denmark. The DNPR has formed the basis for payment of public health care services performed at both public and private hospitals since year 2000 via the Diagnosis Related Groups (DRG)-system in Denmark. It is assumed that registration is complete for these services at both public and private hospitals since 2000. However, for patient paid and private health care insurance paid services performed at private hospitals and clinics reporting is not complete even though this has been mandatory since 2003. In 2008, it was estimated by the Danish National Board of Health that 5% of all private surgeries were missing in the DNPR [74]. Registration of orthopedic procedures has been reported to be correct in 92% of a sample of cases (inpatients and outpatients) and even better for outpatients alone [103]. Arthroscopy codes from public hospitals were recently validated for cartilage injuries of the knee. Registration was correct in 88% of 117 patients [104].

Paper III

Obtaining symptoms from the patient by self-reported questionnaires is less prone to interviewer bias than obtaining clinical history and can not only detect presence of a symptom but also to which degree the symptom bothers the patient (severity). However, there are limitations to the study. The cross-sectional design of paper III did not allow for analysis of predictors of the outcome. Another limitation is the use of RCT baseline data for a cross-sectional study. Randomized trials have strict inclusion and exclusion criteria, and since being set to optimize external validity, included patients are more selected than if data from the full population having meniscus surgery had been included. Early concomitant structural disease was defined as K&L≥1. Commonly, a cut-off point of 2 on the K&L scale is used for radiographic knee OA [76]. K&L grade 1 was used since several studies have shown a strong association between the presence of osteophytes on radiography and the presence of symptomatic knee OA on MRI or by arthroscopic visualization [91].

Paper IV

The SLAMSHAM study has a strong methodological rigor through its design as a double-blinded placebo controlled RCT but there are some limitations. The surgeon's level of experience may differ since general orthopedic surgeons were allowed to operate and not only sports surgeons. However, this has the benefit of an increased external validity. The population in the study is somewhat heterogeneous, from patients with no osteoarthritis to patients with mild osteoarthritis. We do not know whether a meniscus tear has different etiology in those with and without concomitant radiographic OA and how this may affect the result. Moreover, as no consensus exists on what defines a symptomatic meniscus tear we chose to include patients with knee pain and an MRI-confirmed medial meniscus lesion. However, there is a risk that symptoms may actually not be caused by the meniscus tear. Another limitation of using MRI as a diagnostic tool is the risk of a false positive result of a meniscus tear. If the patient will be randomized to a sham operation including a skin incision only, this error will never be discovered. A diagnostic arthroscopy was not performed in the sham group primarily to reduce the risk of deep infection. Other reasons were to avoid any accidental osteochondral lesions from the arthroscope and unwanted intervention from the surgeons.

Increasing annual incidence of APM

The incidence of arthroscopic procedures on the meniscus doubled between the years 2000 and 2011. The large increase began at a time where the evidence for the effect of APM was based on small uncontrolled observational studies, but during the study period several high quality RCT's were published casting doubt on the efficacy of arthroscopy for degenerative knee disease.. The largest increase was seen in the private sector and a financial incentive may have existed. However, the majority of the procedures are still performed in public hospitals. In Denmark, two significant changes in health care policy may have affected the increasing incidence. First, a treatment guarantee was introduced in year 2000, which ensured that patients could be treated at a private hospital if the public hospital was not able to within two months. This was later reduced to one month. Second, since year 2000 all public health care services were paid for according to a DRG rate. The rate increased from 6 502 DKK in year 2000 to 10 483 in 2003 and was relatively stable hereafter (**figure 8**). Payment per procedure potentially provides an incentive for surgeons to perform more treatments (or procedures) because payment is dependent on the quantity of care rather than the quality or outcome of care. Indeed, financial incentives have been shown to increase the surgical rate at private hospitals and clinics [105, 106] and concerns are expressed that this may also be true for public hospitals [74]. In addition, the introduction of a treatment guarantee may erroneously have been interpreted as a surgery guarantee leading to patients receiving surgery as the first treatment choice, before standardized non-surgical treatments were tried and evaluated, or any symptoms were given the chance to remit spontaneously.

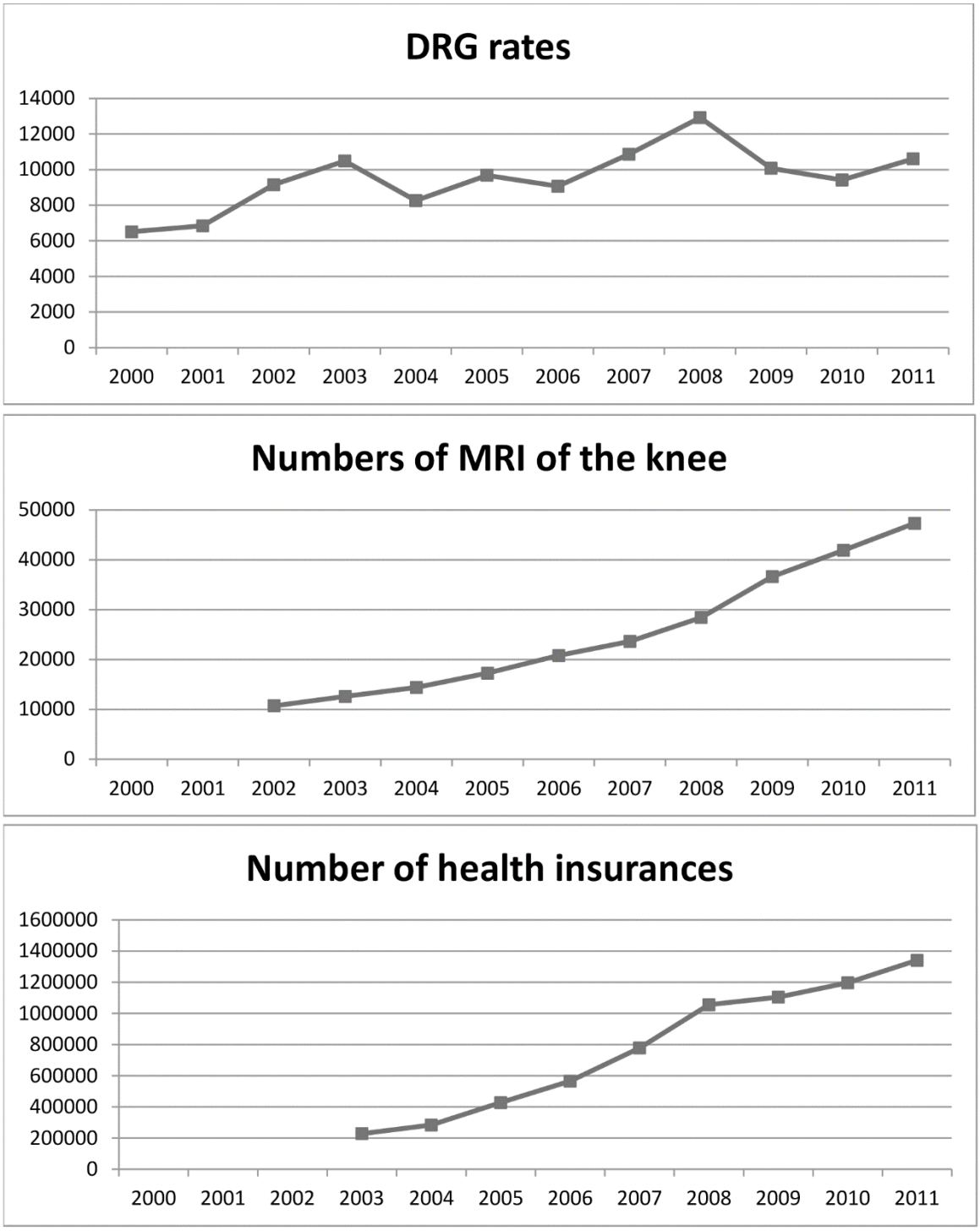


Figure 8 DRG rates and data on number of MRI's of the knee was retrieved from Statens Serum Institut (www.ssi.dk - accessed march 2014). Private health insurance data was retrieved from the branch organization for insurance and pension (www.forsikringogpension.dk).

Other factors relating to the increase may be increased use of private health insurances and the use of knee MRI as a diagnostic tool. Indeed, the proportion of the Danish population having a private health insurance increased from 4 % in 2003 to 24 % in 2011 (**figure 8**). This likely led to easier access to surgery for those with a private health insurance, and patients may be more likely to prefer a costly treatment such as

surgery when covered by health insurance coverage. Providing quick treatment for patients is often considered beneficial for early recovery and prognosis. However, in musculoskeletal conditions where symptoms are known to fluctuate, such as in a degenerative knee disease, quick access to treatment may actually not be advantageous since symptoms could remit without treatment. Indeed, for middle-aged and older patients meniscus surgery most often consists of resection of a degenerative meniscus tear [107]. The knee symptoms patients experience are likely related to knee OA [28] and not the meniscal tear as such. Patients with OA and effectively treated with patient education, physiotherapy and weight loss as first treatments [108].

MRI examinations of the knee are increasingly used in diagnosing meniscus pathology and could influence surgical decision making by detecting meniscus tears in a painful knee. Meniscus tears visualized on MRI provide a persuasive indication for surgery for both surgeon and patient with a painful knee. Indeed, the use of MRI of the knee has increased five-fold between 2002 and 2011 (**figure 8**). However, as earlier mentioned, positive findings on MRI are common also in asymptomatic individuals and even more so in knees with osteoarthritis [1, 109] and the increased use of MRI as a diagnostic tool could lead to overtreatment of patients whose symptoms are not related to a meniscus lesion, but to knee OA.

Even though financial incentives and the (misinterpretation of the) treatment guarantee seem plausible causes for the increased rate of meniscus procedures these causes are unlikely to account for the regional variations since regions share the same national reimbursement and health-care policy. In paper II, large regional differences were present in the provision of arthroscopic meniscus surgery. Regional variations in the provision of surgery are not unknown [15] and reasons for these variations have been discussed [110]. Regional variation may suggest a lack of consensus on when to perform APM or different traditions within each region for preference of surgery. However, a systematic review showed little evidence of difference in beliefs in clinical indications as the cause of regional variations in use of coronary angiography, upper gastrointestinal endoscopy and carotid endarterectomy [111]. High surgical rates in some regions may instead be related to traditions in surgical training or a strong belief in a specific procedure [112, 113]. In this study we found a low incidence of meniscal surgery in Region North but a report on shoulder surgery in Denmark found a high incidence of shoulder arthroscopy in the same region compared to the other regions [114]. It seems there is little correlation in regional rates of procedures even within the same specialty.

The delay in the dissemination, acceptance and implementation of high-level clinical evidence into the practice of arthroscopic surgery call for a need to harmonize the indications of surgery through national guidelines. In 2012, a Danish national clinical guideline for the treatment of knee OA concluded that arthroscopy as a treatment of knee OA was inappropriate [115]. The slightly dropping incidence of arthroscopic procedures on the synovia and cartilage per 100 000 from 305 to 285 from 2012 to 2013 (data accessed on www.ssi.dk, November 2014) may be related to this recommendation. Another approach to harmonize the indications of preference sensitive surgery is the use of decision-making aids. Decision-making aids are evidence-based and educate the patient about the available treatment options. Involving the patient in the decision of treatment was proven efficient in decreasing surgical rates for hip and knee replacement surgery [116]. Revisiting financial reimbursement could be another way of influencing the rate of surgery by simply decreasing or removing the financial incentive for procedures with a high level of evidence for no benefit. Another way to limit the financial incentive especially for private hospitals could be to require health care insurance companies not to reimburse a procedure with no proven benefit over placebo surgery, or no additional benefit compared to non-surgical treatments.

The symptomatic degenerative meniscus tear – does it exist?

Symptoms commonly associated with a traumatic meniscus tear are localized pain, pain when pivoting and mechanical symptoms such as clicking, locking or catching, giving way or difficulty straightening knee. Some of these symptoms are also found to be associated with an MRI-verified degenerative meniscus tears [33-35]. However, many other degenerative knee conditions generate similar symptoms limiting the specificity of these symptoms for a degenerative meniscus tear. Indeed Niu et al. found that the presence of concomitant radiographic knee OA increased the correlation to localized pain, clicking, catching and giving way. In addition, a degenerative meniscus tear may not cause symptoms at all. In the population, 60% of meniscus tears found on MRI are in asymptomatic knees [1]. In paper III, patients eligible for APM (defined as presence of meniscus tear on MRI and knee pain) reported symptoms also commonly present in patients with knee OA. In fact, mechanical symptoms were more common in those with concomitant radiographic structural changes suggesting that knee OA is often the primary cause of symptoms in the presence of a meniscus tear on MRI. Furthermore, there is no evidence to support that those patients reporting mechanical symptoms are more likely to benefit from APM [8, 13] than patients without these symptoms. These findings support previous reports suggesting that a degenerative meniscus tear is an early feature of knee OA [28]. The question is actually if a degenerative meniscus tear in itself cause symptoms at all. More likely, a degenerative meniscus tear should be considered an incidental finding (by MRI or by arthroscopy) in the patient with early or established knee OA. If so, treatment should follow the same guidelines as knee OA. Current recommendations for patients with knee OA start with patient education, physiotherapy and weight loss if needed [108].

Ethical considerations

There are several ethical concerns when performing a placebo controlled surgical trial. The initial precept in medicine is 'Do no harm'. In the placebo procedure, in the SLAMSHAM study, we 'harm' the patients with a skin incision and put them under the risk of general anesthesia. Even though the risk is very small, [117-119] the procedure has no therapeutic effect. So how can it be ethical to perform placebo surgery? On the other hand, we might as well ask ourselves how it can be ethical not to evaluate surgical procedures with the most rigorous study designs. To introduce or continue to perform surgical interventions much more 'harming' than a skin incision without knowing if any therapeutic effect is present at all may be considered unethical. Is it ethical to put patients under general anesthesia and perform a procedure that has no known effect? Indeed the opposite seems quite unethical, and earlier placebo controlled trials have shown the effect a placebo controlled trial can have on already established procedures. A multistep process has been proposed to ensure that sham-controlled surgical trials are performed in an ethical manner [120]: 1) there is uncertainty regarding the therapeutic merits of a particular surgical treatment; 2) There are disagreements about the perceived benefits of a particular procedure compared with the placebo; 3) Benefits might be due to the "experience of surgery" and the postoperative care regimen; 4) Risks are reduced as far as possible in the sham surgery arm without compromising trial design; and 5) there is a lack of a superior alternative therapy. The SLAMSHAM study was designed to meet these conditions (**table 4**).

Conditions for Placebo Surgery	
1	Substantial disability has been shown 3 months after APM and 50% develop knee OA after 10-20 years.
2	A significant placebo effect exists in arthroscopic surgery for knee OA and meniscus tears.
3	Patients can recovery without surgery even those with mechanical symptoms such as catching/locking.
4	Risks are minimized to skin incision and general anaesthesia.
5	Alternative therapies such as medical treatment and/or exercise has not yet shown superiority over the APM procedure.

Table 4 Conditions that makes placebo surgery in the SLAMSHAM study acceptable (adapted from Metha S, Myers TG, Jonner JH, Hufmann GR, Sennet BJ, J Bone J Surg 2007;89:1650-3).

Evidence based treatment of degenerative meniscus tears

Recent placebo controlled orthopedic studies [8, 70, 121] have effectively shown how a placebo-controlled surgical trial can evaluate a given procedure that has been adopted widely, despite an absence of robust evidence.

In paper V, we report that patients were willing to participate in an orthopedic placebo controlled surgical trial. Challenges remain to improve screening procedures for an improved feasibility and pilot studies are critical for a realistic assessment of number needed to screen and number needed to allocate. When recruiting patients for a placebo controlled surgical trial focus should be on the oral information given by an orthopedic surgeon and the patient's contribution to science should be emphasized.

The result of the SLAMSHAM study may either confirm the findings of the FIDELITY study [8] and encourage non-surgical treatment of middle-aged patients with an MRI-verified meniscus tear and mild or no knee osteoarthritis, or oppose these results and support continued use of APM in this patient category. If the results indicate that the efficacy of APM is less than or equal to placebo (and it may do more harm) the continued practice of APM as the treatment of choice in spite of mounting evidence against this procedure would be further discouraged.

Randomized controlled trials are considered gold standard and there are no reasons why orthopedic surgical interventions should be evaluated with case series or observational studies only. This thesis support previous RCT's in showing the need for studies with rigorous design in orthopedics. Preferably, the same set of rules as for pharmaceutical therapies should apply to surgical interventions. One could never imagine a new pharmaceutical agent being introduced without conduct of proper trials. Indeed, there are no pharmaceutical treatments introduced without phase I, II and III studies. While most drug treatments are reversible, a surgical procedure is an irreversible intervention and should be saved for those where non-surgical treatment has failed.

Conclusion

The large increase of arthroscopic procedures on the meniscus contrasts the existing lack of evidence of added benefit of surgery compared to non-surgical interventions, or in comparison to sham surgery. The largest increase in incidence was seen in the private sector even though the public sector still accounted for the largest share of procedures performed. A financial incentive exists for both public and private hospitals in continued use of this procedure. Regional variation in provision of meniscus surgery may be caused by a lack of consensus on the indications for arthroscopic meniscus surgery. Meniscus symptoms such as catching or locking are generally taken as an indication for meniscus surgery, but catching was rarely reported prior to surgery in middle-aged patients deemed eligible for surgery. The evidence for the relation of catching symptoms to a meniscus tear or an added benefit from partial meniscectomy in patients with these symptoms is scanty. The increased frequency of catching in those with concomitant signs of radiographic structural disease supports the notion that a symptomatic degenerative meniscal tear is an early sign of knee osteoarthritis. Most likely, neither mechanical nor other symptoms are attributed to the degenerative meniscal tear as such, but rather to the ongoing degenerative process. The result of the ongoing SLAMSHAM study may either further support these findings or suggest that APM is a viable treatment option. Well-known challenges in recruiting patients for surgical trials have been confirmed in this patient group. Even though patients are willing to participate in randomized trials, the addition of a placebo component adds to the recruitment challenges.

Future perspectives

National guidelines and decision aids are warranted to improve uptake of treatment guideline recommendations and to avoid potential unnecessary surgery and reduce regional variation. The use of APM in Denmark as a treatment for degenerative meniscus tears in middle-aged and older patients with concomitant knee OA is already recommended against in national clinical guidelines. To encourage the most appropriate use of this procedure further efforts at implementation are needed. This may include audits and changes in financial incentives for a procedure of no proven benefit. In addition, health care insurance companies' need to take into account evidence of efficacy and harms for different treatments, including surgical procedures, when deciding on what treatments to reimburse.

The findings of no added benefit of APM compared to non-surgical interventions for patients with a degenerative meniscus tear of the knee challenges our view on other surgeries for degenerative conditions as well. These include shoulder and hip arthroscopy and miscellaneous hand and foot surgeries. These procedures should be examined in future well-designed and placebo-controlled RCT's. Orthopedic surgeons should continue to strive for high-level evidence of all procedures. Placebo controlled trials are feasible and can effectively demonstrate the efficacy of a surgical intervention [122]. When deciding upon treatment, the surgeon should take the evidence of benefits and harms for available treatments into account and together with decision making aids and a well-informed patient decide on the treatment strategy that fits best with the individual patients preferences and needs [123].

Acknowledgements

This thesis was accomplished with the help of several people to whom I would like to express my gratitude:

All *patients* for willingly participating in a placebo controlled surgical trial.

Ewa M. Roos, my main supervisor, for teaching me strong scientific methodology, for always quick and comprehensive email replies and for allowing me a great degree of freedom in my PhD work.

Stefan Lohmander, my co-supervisor, for always kean observations and for teaching me to tell the story.

Jonas B. Thorlund, my friend and colleague for advise and help of almost every practical and scientific aspect of this PhD and being a great roomy on several occasion.

Karl Rønne, Søren Bondo, Anders Kunov, Thomas Houe, Peter Jessen, Peter Bentzon, Jawaid Ahmed, Michael Langergaard and Per Falkenberg for daring to perform a placebo procedure.

Robin Christensen for statistical input.

Christina Schou, *Tejs Bryggers* and *Janne Mølgård* for endless testing of patients.

The outpatient clinics in *Department of Orthopedic*, *Slagelse and Næstved Hospital* for housing me and providing room and staff for including patients. Great thanks to *Mette Haugaard* for finding time to service me on top of her already overloaded work.

Nina J. Kise, May Arna and Silje Stensrud for welcoming me in Oslo and collaboration on baseline data.

Research Unit for Musculoskeletal Function and Physiotherapy (FOF), for several meetings, discussions and teachings on scientific methodology, strategy, and numerous other subjects.

My wife for strong support and never once complaining about all the hours I have spend in my work cave in the cellar.

This thesis was supported with grants from Research Unit Næstved/Slagelse/Ringsted Hospitals, Region Zealand Health Research Fund, Henrik and Edith Henriksens Memorial Fund and Gigtforeningen.

References

1. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT: **Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons**. *N Engl J Med* 2008, **359**(11):1108-1115.
2. Cullen K, Hall M, Golosinskiy A: **Ambulatory surgery in the United States, 2006**. *National health statistics reports, National Center for Health Statistics* 2009, **11**:1-28.
3. Kim S: **Increase in Outpatient Knee Arthroscopy in the United States: A Comparison of National Surveys of Ambulatory Surgery, 1996 and 2006**. *J Bone Joint Surg* 2011, **93**(11):994.
4. Fairbank TJ: **Knee joint changes after meniscectomy**. *J Bone Joint Surg* 1948, **30b**(4):664-670.
5. Hamberg P, Gillquist J, Lysholm J: **A comparison between arthroscopic meniscectomy and modified open meniscectomy. A prospective randomised study with emphasis on postoperative rehabilitation**. *J Bone Joint Surg* 1984, **66**(2):189-192.
6. Hede A, Hejgaard N, Larsen E: **Partial or total open meniscectomy? A prospective, randomized study**. *Int Orthop* 1986, **10**(2):105-108.
7. Lyman: **Surgical Decision Making for APM**. *Arthroscopy* 2012.
8. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TLN: **Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear**. *N Engl J Med* 2013, **369**(26):2515-2524.
9. Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH *et al*: **Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis**. *N Engl J Med* 2013, **368**(18):1675-1684.
10. Herrlin SV, Wange PO, Lapidus G, Hållander M, Werner S, Weidenhielm L: **Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up**. *Knee Surg Sports Traumatol Arthrosc* 2013, **21**(2):358-364.
11. Lim HC, Bae JH, Wang JH, Seok CW, Kim MK: **Non-operative treatment of degenerative posterior root tear of the medial meniscus**. *Knee Surg Sports Traumatol Arthrosc* 2009, **18**(4):535-539.
12. Herrlin S, Hållander M, Wange P, Weidenhielm L, Werner S: **Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial**. *Knee Surg Sports Traumatol Arthrosc* 2007, **15**(4):393-401.
13. Gauffin H, Tagesson S, Meunier A, Magnusson H, Kvist J: **Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study**. *Osteoarthritis Cartilage* 2014, **22**(11):1808-1816.
14. Khan M, Evaniew N, Bedi A, Ayeni OR, Bhandari M: **Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis**. *CMAJ* 2014, **186**(14):1054-1064.
15. McPherson K, Wennberg JE, Hovind OB, Clifford P: **Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway**. *N Engl J Med* 1982, **307**(21):1310-1314.

16. **The NHS atlas of variation in healthcare: reducing unwarranted variation to increase value and improve quality**. In. www.rightcare.nhs.uk/atlas/qipp_nhsAtlas-LOW_261110c.pdf (accessed Nov 11, 2013); 2010.
17. Fox AJ, Wanivenhaus F, Burge AJ, Warren RF, Rodeo SA: **The human meniscus: A review of anatomy, function, injury, and advances in treatment**. *Clinical anatomy (New York, NY)* 2014.
18. Clark CR, Ogden JA: **Development of the menisci of the human knee joint. Morphological changes and their potential role in childhood meniscal injury**. *J Bone Joint Surg* 1983, **65**(4):538-547.
19. Thompson WO, Thaete FL, Fu FH, Dye SF: **Tibial meniscal dynamics using three-dimensional reconstruction of magnetic resonance images**. *Am J Sports Med* 1991, **19**(3):210-215; discussion 215-216.
20. Arnozcky SP, Warren RF: **Microvasculature of the human meniscus**. *Am J Sports Med* 1982, **10**(2):90-95.
21. Assimakopoulos AP, Katonis PG, Agapitos MV, Exarchou EI: **The innervation of the human meniscus**. *Clin Orthop Relat Res* 1992(275):232-236.
22. Mine T, Kimura M, Sakka A, Kawai S: **Innervation of nociceptors in the menisci of the knee joint: an immunohistochemical study**. *Arch Orthop Trauma Surg* 2000, **120**(3-4):201-204.
23. Sweigart MA, Athanasiou KA: **Toward tissue engineering of the knee meniscus**. *Tissue engineering* 2001, **7**(2):111-129.
24. Fithian DC, Kelly MA, Mow VC: **Material properties and structure-function relationships in the menisci**. *Clin Orthop Relat Res* 1990(252):19-31.
25. Voloshin AS, Wosk J: **Shock absorption of meniscectomized and painful knees: a comparative in vivo study**. *JournalBiomed Eng* 1983, **5**(2):157-161.
26. Levy IM, Torzilli PA, Warren RF: **The effect of medial meniscectomy on anterior-posterior motion of the knee**. *J Bone Joint Surg* 1982, **64**(6):883-888.
27. Shoemaker SC, Markolf KL: **The role of the meniscus in the anterior-posterior stability of the loaded anterior cruciate-deficient knee. Effects of partial versus total excision**. *J Bone Joint Surg* 1986, **68**(1):71-79.
28. Englund M, Roemer FW, Hayashi D, Crema MD, Guermazi A: **Meniscus pathology, osteoarthritis and the treatment controversy**. *Nature Rev Rheumatol* 2012, **8**(7):412-419.
29. Nielsen AB, Yde J: **Epidemiology of acute knee injuries: a prospective hospital investigation**. *J Trauma* 1991, **31**(12):1644-1648.
30. Englund M, Niu J, Guermazi A, Roemer FW, Hunter DJ, Lynch JA, Lewis CE, Torner J, Nevitt MC, Zhang YQ *et al*: **Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness**. *Arthritis & Rheumatism* 2007, **56**(12):4048-4054.
31. Bhattacharyya T, Gale D, Dewire P, Totterman S, Gale ME, McLaughlin S, Einhorn TA, Felson DT: **The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee**. *J Bone Joint Surg* 2003, **85-a**(1):4-9.

32. Snoeker BA, Bakker EW, Kegel CA, Lucas C: **Risk factors for meniscal tears: a systematic review including meta-analysis**. *J Orthop Sports Phys Ther* 2013, **43**(6):352-367.
33. Niu NN, Losina E, Martin SD, Wright J, Solomon DH, Katz JN: **Development and preliminary validation of a meniscal symptom index**. *Arthritis Care & Research* 2011, **63**(2):208-215.
34. Yan R, Wang H, Yang Z, Ji ZH, Guo YM: **Predicted probability of meniscus tears: comparing history and physical examination with MRI**. *Swiss Medical Weekly* 2011, **141**:w13314.
35. Wagemakers HP, Heintjes EM, Boks SS, Berger MY, Verhaar JA, Koes BW, Bierma-Zeinstra SM: **Diagnostic Value of History-taking and Physical Examination for Assessing Meniscal Tears of the Knee in General Practice**. *Clin J Sport Med* 2008, **18**:24-30.
36. Hegedus EJ: **Physical Examination Tests for Assessing a Torn Meniscus in the Knee: A Systematic Review With Meta-analysis**. *J Orthop Sports Phys Ther* 2007, **37**:541-550.
37. Shrier I, Boudier- Revéret M, Fahmy K: **Understanding the Different Physical Examination Tests for Suspected Meniscal Tears**. *Curr Sports Med Rep* 2010, **9**(5):284-289.
38. Konan S, Rayan F, Haddad FS: **Do physical diagnostic tests accurately detect meniscal tears?** *Knee Surg Sports Traumatol Arthrosc* 2009, **17**(7):806-811.
39. Meserve BB, Cleland JA, Boucher TR: **A meta-analysis examining clinical test utilities for assessing meniscal injury**. *Clin Rehabil* 2008, **22**:143-161.
40. Ryzewicz M, Peterson B, Siparsky PN, Bartz RL: **The Diagnosis of Meniscus Tears**. *Clin Orthop Relat Res* 2007, **455**:123-133.
41. Fox MG: **MR Imaging of the Meniscus: Review, Current Trends, and Clinical Implications**. *Radiologic Clinics of North America* 2007, **45**(6):1033-1053.
42. Jackson RW, Rouse DW: **The Result of Partial Arthroscopic Meniscectomty in Patients Over 40 Years of Age**. *J Bone Joint Surg* 1982, **64-B**(4):481-485.
43. McBride GG, Constine RM, VCarson RW: **Arthroscopic partial medial meniscectomy in the older patient**. *J Bone Joint Surg* 1984, **66**:547-551.
44. Boe S, Hansen H: **Arthroscopic partial meniscectomy in patients aged over 50**. *British Editorial Society of Bone and Joint Surgery* 1986, **68**(5):707.
45. Faunø P, Nielsen AB: **Arthroscopic Partial Meniscectomy: A Long-Term Follow-up**. *Arthroscopy* 1992, **8**(3):345-349.
46. Bonamo JJ, Kessler KJ, Noah J: **Arthroscopic meniscectomy in patients over the age of 40**. *Am J Sports Med* 1992, **20**(4):422-429.
47. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP: **A controlled trial of arthroscopic surgery for osteoarthritis of the knee**. *N Engl J Med* 2002, **347**(2):81-88.
48. Kirkley A, Birmingham TB, Litchfield RB, Giffin R, Willits KR, Wong CJ, Feagan BG, Donner A, Griffin SH, D'Ascanio LM *et al*: **A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee**. *N Engl J Med* 2008, **359**(11):1097-1107.

49. Yim JH, Seon JK, Song EK, Choi JI, Kim MC, Lee KB, Seo HY: **A Comparative Study of Meniscectomy and Nonoperative Treatment for Degenerative Horizontal Tears of the Medial Meniscus**. *Am J Sports Med* 2013, **41**(7):1565-1570.
50. Suter LG, Fraenkel L, Losina E, Katz JN, Gomoll AH, Paltiel AD: **Medical decision making in patients with knee pain, meniscal tear, and osteoarthritis**. *Arthritis & Rheumatism* 2009, **61**(11):1531-1538.
51. Seedhom B, Hargreaves D: **Transmission of the load in the knee joint with special reference to the role of the meniscus. Part I-II.** *Eng Med* 1979, **4**:207–228.
52. Fukubayashi T, Kurosawa H: **The contact area and pressure distribution pattern of the knee. A study of normal and osteoarthrotic knee joints**. *Acta orthopaedica Scandinavica* 1980, **51**(6):871-879.
53. Englund M, Lohmander LS: **Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy**. *Arthritis & Rheumatism* 2004, **50**(9):2811-2819.
54. Papalia R, Del Buono A, Osti L, Denaro V, Maffulli N: **Meniscectomy as a risk factor for knee osteoarthritis: a systematic review**. *British Medical Bulletin* 2011, **99**(1):89-106.
55. Englund M, Guermazi A, Roemer FW, Aliabadi P, Yang M, Lewis CE, Torner J, Nevitt MC, Sack B, Felson DT: **Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The multicenter osteoarthritis study**. *Arthritis & Rheumatism* 2009, **60**(3):831-839.
56. Wai EK, Kreder KJ, Williams JI: **Arthroscopic Débridement of the Knee for Osteoarthritis in Patients Fifty Years of Age or Older**. *J Bone Joint Surg* 2002, **84A**(1):17-22.
57. Valdes AM, Suokas AK, Doherty SA, Jenkins W, Doherty M: **History of knee surgery is associated with higher prevalence of neuropathic pain-like symptoms in patients with severe osteoarthritis of the knee**. *Seminars in arthritis and rheumatism* 2014, **43**(5):588-592.
58. Salzler MJ, Lin A, Miller CD, Herold S, Irrgang JJ, Harner CD: **Complications after arthroscopic knee surgery**. *Am J Sports Med* 2014, **42**(2):292-296.
59. Noble J, Ilango B, Obeid M: **Complications of arthroscopy of the knee**. *The Knee* 1998, **5**:1-8.
60. Bohensky MA, Ademi Z, deSteiger R, Liew D, Sundararajan V, Bucknill A, Kondogiannis C, Brand CA: **Quantifying the excess cost and resource utilisation for patients with complications associated with elective knee arthroscopy: a retrospective cohort study**. *The Knee* 2014, **21**(2):491-496.
61. Lim HC, Adie S, Naylor JM, Harris IA: **Randomised trial support for orthopaedic surgical procedures**. *PLoS One* 2014, **9**(6):e96745.
62. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien P-A, Reeves BC, Seiler CM: **Challenges in evaluating surgical innovation**. *The Lancet* 2009, **374**(9695):1097-1104.
63. McLeod RS: **Issues in Surgical Randomized Controlled Trials**. *World J Surg* 1999, **23**(12):1210-1214.
64. London AJ, Kadane JB: **Placebo that harms: sham surgery controls in clinical trials**. *Stat Methods Med Res* 2002, **11**(5):413-427.
65. Macklin R: **The Ethcial Problems of Sham Surgery in Clinical Trials**. *N Engl J Med* 1999, **341**(13):992-996.

66. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ: **Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome**. *PLoS One* 2010, **5**(12):e15591.
67. Wechsler ME, Kelley JM, Boyd IOE, Dutile S, Marigowda G, Kirsch I, Israel E, Kaptchuk TJ: **Active Albuterol or Placebo, Sham Acupuncture, or No Intervention in Asthma**. *N Engl J Med* 2011, **365**:119-126.
68. Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, Frede S, Canbay AE, Michel MC, Heemann U, Schedlowski M: **Behavioral conditioning of immunosuppression is possible in humans**. *FASEB J* 2002, **16**:1869-1873.
69. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S: **A Placebo-Controlled Surgical Trial of the Treatment of Migraine Headaches**. *Plastic and Reconstructive Surgery* 2009, **124**(2):461-468.
70. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt CJ, Graves SE, Staples MP, Murphy B: **A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures**. *N Engl J Med* 2009, **361**(6):557-568.
71. Dimond EG, Kittle CF, Crockett JE: **Comparison of internal mammary artery ligation and sham operation for angina pectoris**. *American J Cardiol* 1960, **5**:483-486.
72. Finnis DG, Kaptchuk TJ, Miller F, Benedetti F: **Biological, clinical, and ethical advances of placebo effects**. *The Lancet* 2010, **375**:686-695.
73. Doherty M, Dieppe P: **The "placebo" response in osteoarthritis and its implications for clinical practice**. *Osteoarthritis Cartilage* 2009, **17**(10):1255-1262.
74. Lynge E, Sandegaard JL, Rebolj M: **The Danish National Patient Register**. *Scand J Public Health* 2011, **39**(7 Suppl):30-33.
75. Pedersen CB: **The Danish Civil Registration System**. *Scand J Public Health* 2011, **39**(7 Suppl):22-25.
76. Kellgren JH, Lawrence JS: **Radiological Assessment of Osteoarthrosis**. *Ann Rheum Dis* 1957, **16**(4):494-502.
77. Schiphof D, de Klerk B, Kerkhof H, Hofman A, Koes B, Boers M, Bierma-Zeinstra S: **Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis**. *Ann Rheum Dis* 2011, **70**(8):1422-1427.
78. Stensrud S, Roos EM, Risberg MA: **A 12-Week Exercise Therapy Program in Middle-Aged Patients With Degenerative Meniscus Tears: A Case Series With 1-year Follow-up**. *J Orthop Sports Phys Ther* 2012, **42**(11):919-931.
79. Stensrud S, Risberg MA, Roos EM: **Knee function and knee muscle strength in middle-aged patients with degenerative meniscal tears eligible for arthroscopic partial meniscectomy**. *Br J Sports Med* 2014, **48**(9):784-788.
80. Stensrud S, Risberg MA, Roos EM: **Effect of Exercise Therapy Compared with Arthroscopic Surgery on Knee Muscle Strength and Functional Performance in Middle-Aged Patients with Degenerative Meniscus Tears: A 3-Mo Follow-up of a Randomized Controlled Trial**. *Am J Phys Med Rehab* 2014.

81. Roos EM, Lohmander LS: **The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis**. *Health Qual Life Outcomes* 2003, **1**:64.
82. Schulz KF, Altman DG, Moher D: **CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials**. *BMJ* 2010, **340**(mar23 1):c332-c332.
83. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD: **Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure**. *J Orthop Sports Phys Ther* 1998, **28**(2):88-96.
84. Ware JE, Sherbourne CD: **The MOS 36-item Short-Form Health Survey (SF-36): I. Conceptual Frame and Item Selection**. *Med Care* 1992, **30**(6):473-483.
85. McHorney CA, Ware JE, Raczek AE: **The MOS 35-item Short Form Health Survery (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs**. *Med Care* 1993, **31**(3):247-263.
86. Group TE: **Euroqol - a new facility for the measurement of health-related quality of life**. *Health Policy* 1990, **16**:199-208.
87. Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM: **Generation of a Danish TTO value set for EQ-5D health states**. *Scand J Public Health* 2009, **37**(5):459-466.
88. Charles HC, Kraus VB, Ainslie M, Hellio Le Graverand-Gastineau MP: **Optimization of the fixed-flexion knee radiograph**. *Osteoarthritis Cartilage* 2007, **15**(11):1221-1224.
89. Kothari M, Guermazi A, Ingersleben G, Miaux Y, Sieffert M, Block J, Stevens R, Peterfy C: **Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis**. *European Radiology* 2004, **14**(9):1568-1573.
90. Altman R, Gold G: **Atlas of individual radiographic features in osteoarthritis, revised1**. *Osteoarthritis Cartilage* 2007, **15**:A1-A56.
91. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS *et al*: **EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis**. *Ann Rheum Dis* 2010, **69**(3):483-489.
92. Kijowski R: **Arthroscopic Validation of Radiographic Grading Scales of Osteoarthritis of the Tibiofemoral Joint**. *AJR American journal of roentgenology* 2006, **187**(3):794-799.
93. Gudbergsen H, Lohmander LS, Jones G, Christensen R, Bartels EM, Danneskiold-Samsøe B, Bliddal H, Boesen M: **Correlations between radiographic assessments and MRI features of knee osteoarthritis – a cross-sectional study**. *Osteoarthritis Cartilage* 2012.
94. Noyes FR BS, Mangine RE: **Abnormal lower limb symmetry determined by function hop tests after anterior cruciate ligament rupture**. *Am J Sports Med* 1991, **19**:513-518.
95. Tegner Y, Lysholm J, Lysholm M, Gillquist J: **A performance test to monitor rehabilitation and evaluate anterior cruciate ligament injuries**. *Am J Sports Med* 1986, **14**(2):156-159.
96. Bremander AB, Dahl LL, Roos EM: **Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis**. *Scand J Med Sci Sports* 2006, **17**(0):120-127.

97. Thorborg K, Petersen J, Magnusson SP, Hölmich P: **Clinical assessment of hip strenght using a hand-held dynamometer is reliable**. *Scand J Med Sci Sports* 2009, **20**(3):493-501.

98. Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T: **Loss of Knee-Extension Strength Is Related to Knee Swelling After Total Knee Arthroplasty**. *Arch Phys Med Rehabil* 2010, **91**(11):1770-1776.

99. Roy M-AG, Doherty TJ: **Reliability of Hand-Held Dynamometry in Assessment of Knee Extensor Strength After Hip Fracture**. *Am J Phys Med Rehab* 2004, **83**(11):813-818.

100. Rembold CM: **Number needed to screen: development of a statistic for disease screening**. *BMJ* 1998, **317**(7154):307-312.

101. Nelson HD, Helfand M, Woolf SH, Allan JD: **Screening for Postmenopausal Osteoporosis: A Review of the Evidence for the U.S. Preventive Service Task Force**. *Ann Intern Med* 2002, **137**(6):529-541.

102. Frobell R, Lohmander L, Roos E: **The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment**. *Contemp Clin Trials* 2007, **28**(3):295-302.

103. Lass P, Lilholt J, Thomsen L, Lundbye-Christensen S, Enevoldsen H, Simonsen OH: **Kvaliteten af diagnose- og procedurekodning i Ortopædkirurgi Nordjylland**. *Ugeskr Læger* 2006, **168**(48):4212-4215.

104. Mor A, Grijota M, Norgaard M, Munthe J, Lind M, Deruaz A, Pedersen AB: **Trends in arthroscopy-documented cartilage injuries of the knee and repair procedures among 15-60-year-old patients**. In: *Scand J Med Sci Sports.* 2014/09/30 edn; 2014.

105. Hollingsworth JM, Ye Z, Strope SA, Krein SL, Hollenbeck AT, Hollenbeck BK: **Physician-ownership of ambulatory surgery centers linked to higher volume of surgeries**. *Health Aff* 2010, **29**(4):683-689.

106. Mitchell JM: **Effect of physician ownership of specialty hospitals and ambulatory surgery centers on frequency of use of outpatient orthopedic surgery**. *Arch Surg* 2010, **145**(8):732-738.

107. Thorlund JB, Hare KB, Lohmander LS: **Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011**. *Acta Orthop* 2014, **85**(3):287-292.

108. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, Doherty M, Geenen R, Hammond A, Kjeken I *et al*: **EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis**. *Ann Rheum Dis* 2013, **72**(7):1125-1135.

109. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T, Aliabadi P, McLennan CE, Felson DT: **Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study)**. *BMJ* 2012, **29**(345):e5339.

110. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE: **Understanding of regional variation in the use of surgery**. *The Lancet* 2013, **382**(9898):1121-1129.

111. Keyhani S, Falk R, Bishop T, Howell E, Korenstein D: **The Relationship Between Geographic Variations and Overuse of Healthcare Services: A Systematic Review**. *Med Care* 2012, **50**(3):257-261.

112. Chassin MR: **Explaining geographic variations. The enthusiasm hypothesis**. *Med Care* 1993, **31**(5 Suppl):37-44.

113. Bederman SS, Coyte PC, Kreder HJ, Mahomed NN, McIsaac WJ, Wright JG: **Who's in the driver's seat? The influence of patient and physician enthusiasm on regional variation in degenerative lumbar spinal surgery: a population-based study**. *Spine* 2011, **36**(6):481-489.

114. Løvschall C, Witt F, Svendsen S, Hartvigsen J, Johannsen H, Beck S, Kjølby M: **Medicinsk teknologivurdering af kirurgisk behandling af patienter med udvalgte og hyppige skulderlidelser.** *Århus: MTV og Sundhedstjenesteforskning, Region Midtjylland* 2011.

115. **Knæartrose – nationale kliniske retningslinjer og faglige visitationsretningslinjer**. In.: Sundhedsstyrelsen; 2012.

116. Arterburn D, Wellman R, Westbrook E, Rutter C, Ross T, McCulloch D, Handley M, Jung C: **Introducing decision aids at Group Health was linked to sharply lower hip and knee surgery rates and costs**. *Health Aff* 2012, **31**(9):2094-2104.

117. Braz LG, Braz DG, Cruz DSd, Fernandes LA, Módolo NSP, Braz JRC: **Mortality in anesthesia: a systematic review**. *Clinics* 2009, **64**(10):999-1006.

118. Hove LD, Stelnmetz J, Christoffersen JK, Møller A, Nielsen J, Schmidt H: **Analysis of Deaths Related to Anesthesia in the Period 1996–2004 from Closed Claims Registered by the Danish Patient Insurance Association**. *Anesthesiology* 2007, **106**:675-680.

119. Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: **Survey of Anesthesia-related Mortality in France**. *Anesthesiology* 2006, **105**:1087-1097.

120. Mehta S, Myers TG, Lonner JH, Huffman GR, Sennett BJ: **The Ethics of Sham Surgery in Clinical Orthopaedic Research**. *J Bone Joint Surg* 2007, **89**(7):1650-1653.

121. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S *et al*: **A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures**. *N Engl J Med* 2009, **361**(6):569-579.

122. Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJ, Rombach I, Brindley D, Savulescu J, Beard DJ, Carr AJ: **Use of placebo controls in the evaluation of surgery: systematic review**. *BMJ* 2014, **348**:g3253.

123. Hoffmann TC, Montori VM, Del Mar C: **The connection between evidence-based medicine and shared decision making**. *Jama* 2014, **312**(13):1295-1296.

PAPERS I-V

Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011

Jonas B Thorlund[1], Kristoffer B Hare[1, 2], and L Stefan Lohmander[1, 3, 4]

[1]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense; [2]Department of Orthopedics, Slagelse Hospital, Region Zealand, Slagelse; [3]Department of Orthopedics and Traumatology, Odense University Hospital, Odense, Denmark; [4]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden.
Correspondence: jthorlund@health.sdu.dk
Submitted 13-12-11. Accepted 14-03-18

Background — Arthroscopic meniscal surgery is the most common orthopedic procedure, and the incidence has increased in Denmark over the last 10 years. Concomitantly, several randomized controlled trials have shown no benefit of arthroscopic procedures including arthroscopic partial meniscectomy in middle-aged and older individuals suffering from knee pain with or without knee osteoarthritis. We examined the annual incidence of meniscal procedures together with age, sex, and diagnosis for patients who underwent meniscal procedures in the period 2000–2011 in Denmark.

Methods — Data on age, sex, diagnosis, and surgical procedures were extracted from the Danish National Patient Register for the years 2000–2011, for all records containing meniscal surgery as a primary or secondary procedure.

Results — The overall annual incidence of meniscal procedures per 100,000 persons in Denmark doubled from 164 in 2000 to 312 in 2011 (i.e. 8,750 procedures to 17,368 procedures). A 2-fold increase was found for patients aged between 35 and 55, and a 3-fold increase was found for those older than 55. Middle-aged and older patients accounted for 75% of all 151,228 meniscal procedures carried out between 2000 and 2011.

Interpretation — The incidence of meniscal procedures performed in Denmark doubled from 2000 to 2011, with the largest increase in middle-aged and older patients. This increase contrasts with the mounting evidence showing no added benefit of arthroscopic partial meniscectomy over non-surgical treatments. Our observations illustrate the long delay in the dissemination, acceptance, and implementation of research evidence into the practice of arthroscopic surgery.

About 1 million arthroscopic knee procedures were performed in 2006 in the USA, of which at least 700,000 were meniscal resections (Cullen et al. 2009). Numbers from Sweden confirm that meniscal procedures are the most common arthroscopic knee procedures (Roos and Lohmander 2009). The Danish media have reported an increased frequency of meniscal procedures over recent years in Denmark, but the precise numbers, sex, and age distribution of the patients and underlying diagnoses have not been reported. In the same time period, several large, high-quality randomized controlled trials (Moseley et al. 2002, Herrlin et al. 2007, Kirkley et al. 2008) have failed to show any benefit of arthroscopic procedures including arthroscopic partial meniscectomy (APM) for middle-aged and older patients suffering from knee pain with or without concomitant features of radiographic knee osteoarthritis (OA) (Table 1).

Previous reports on the frequency of meniscal procedures have either been based on estimation from a number of hospitals (Cullen et al. 2009) or from insurance databases (Abrams et al. 2013). In Denmark, on the other hand, there is a national database on all healthcare procedures performed in public and private hospitals and clinics (Lynge et al. 2011). In addition, all Dasnish residents are registered in the Civil Registration System (Pedersen 2011) and population demographics are publicly available on the internet through Danish Statistics. This allows calculation of annual incidence rates for meniscal procedures based on the entire Danish population.

We examined the number of meniscal procedures performed in Denmark in the years between 2000 and 2011. We also examined age and sex distribution and the diagnosis registered for the patients undergoing these procedures, using data from the Danish National Patient Register.

Patients and methods

The Danish National Patient Register

All patient contacts with public and private hospitals and clin-

DOI 10.3109/17453674.2014.919558

Table 1. Randomized controlled trials comparing arthroscopy including arthroscopic partial meniscectomy with non-surgical interventions

Author and year	Age and OA entry criteria	Intervention groups (n)	Baseline age, mean (SD)	Results (primary outcome)
Moseley et al. 2002	≤ 75 y, OA (ACR criteria)	1) Arthroscopic lavage (61) 2) Arthroscopic debridement including APM (59) 3) Placebo surgery (60)	51.2 (10.5) 53.6 (12.2) 52.0 (11.1)	No difference between groups on Knee-Specific Pain Scale Score at 24-month follow-up
Herrlin et al. 2007 Herrlin et al. 2013	45–64 y, OA grade 0 or 1 (Ahlbäck classification)	1) APM + exercise (47) 2) Exercise (43)	54 57	No difference between groups in KOOS scores at 6-month follow-up No difference between groups in KOOS scores at 60-month follow-up
Kirkley et al. 2008	≥ 18 y, OA grade ≥2 (K&L classification)	1) Arthroscopic surgery including APM + physical and medical therapy (92) 2) Physical and medical therapy (86)	58.6 (10.2) 60.6 (9.9)	No difference between groups in WOMAC scores at 24-month follow-up
Katz et al. 2013	≥ 45 y, OA on MRI (defined as cartilage defects) or radiographs	1) APM + physical therapy (161) 2) Physical therapy (169)	59.0 (7.9) 57.8 (6.8)	No difference between groups in WOMAC physical-function score at 6-month follow-up
Yim et al. 2013	No age criteria, OA grade 0 or 1 (K&L classification)	1) APM + home exercise program (50) 2) 3 weeks supervised rehabilitation program + home exercise program (52)	54.9 (10.3) 57.6 (11.0)	No difference between groups in Lysholm score at 24-month follow-up
Sihvonen et al. 2013	35–65 y, OA grade 0 or 1 (K&L classification)	1) APM (70) 2) Placebo surgery (76)	52 (7) 52 (7)	No difference between groups in Lysholm score, WOMET score, and knee pain after exercise at 12-month follow-up

ACR: American College of Rheumatology; APM: Arthroscopic Partial Meniscectomy; K&L: Kellgren and Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score; OA: Osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; WOMET: Western Ontario Meniscal Evaluation Tool.

ics in Denmark are registered in the Danish National Patient Register (DNPR) (Lynge et al. 2011). Administrative data include the unique personal identification number (the Central Person Register (CPR) number (Pedersen 2011), given to all residents of Denmark and registered in the Civil Registration System), hospital identification, date and time of activity, and patient's municipality (among other characteristics). Clinical data include types of surgical procedures (according to the Nordic Classification of Surgical Procedures (NCSP)) and diagnosis (International Classification of Diseases (ICD-10)). A unique record number can be used to identify each patient contact with the hospital. This record number can be combined with the CPR number to track individual patient contacts within the hospital system.

Since 2000, the DNPR has formed the basis of payment of public and private hospital services via the Diagnostic Related Group (DRG) system (Lynge et al. 2011). It is assumed that registration is complete for public hospitals since 2000. For private hospitals and clinics, however, it is known that reporting is not complete, even though this has been mandatory since 2003. In 2008, it was estimated by the Danish National Board of Health that 5% of all private operations were missing in the DNPR (Lynge et al. 2011). Registration of orthopedic procedures has been reported to be correct in 92% of a sample of cases (inpatients and outpatients), and even better for outpatients alone, whereas numbers were lower for registration of diagnoses (primary diagnoses 83% and secondary diagnoses 77%), but again with better numbers for outpatients (Lass et al. 2006).

Study sample

Data were extracted from the DNPR on all record numbers containing a procedure code(s) for meniscal surgery (KNGD and all sub-codes) as the primary procedure or as part of other surgery in the twelve-year period 2000–2011. For each record, information was extracted on age, sex, diagnosis (primary and secondary), and surgical procedures in addition to meniscal surgery. The CPR number was used to track patients with several meniscal operations (defined as surgery on separate dates) during the study period. For patients with several surgery dates, it could not be determined whether surgery was carried out on the same knee—as left or right side is not registered systematically in the DNPR.

Definitions

Primary surgical procedure: meniscal surgery was considered the primary surgical procedure if the procedure was coded as "V" (V = most important surgical procedure in a finished contact) or "P" (P = most important procedure during a given surgery). Secondary surgical procedure: meniscal surgery was considered a secondary surgical procedure if it was coded as "D" (D = secondary procedure, part of a surgery without being the primary procedure). Thus, several surgical procedures could be conducted at the same surgery. Primary diagnosis:

Table 2. Number of meniscal procedures (all codes) and incidence rate of meniscal procedures per year from 2000 through 2011, gender distribution, and mean age at surgery per year

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Procedures:													
< 35 years, n	3,085	3,020	3,210	3,124	3,036	2,963	2,987	2,971	2,860	3,440	3,706	3,622	38,024
35–55 years, n	4,155	4,440	5,038	5,408	5,567	5,765	5,792	6,399	6,547	8,493	8,765	8,636	75,005
> 55 years, n	1,510	1,675	2,121	2,335	2,468	2,846	2,966	3,482	3,703	4,682	5,301	5,110	38,199
Total, n	8,750	9,135	10,369	10,867	11,071	11,574	11,745	12,852	13,110	16,615	17,772	17,368	151,228
Men, %	64	62	63	62	61	61	60	60	59	60	58	59	60
Women, %	36	38	37	38	39	39	40	40	41	40	42	41	40
Mean age at surgery	41	42	43	43	44	44	45	46	46	46	47	47	45
CI	41–42	41–42	42–43	43–44	43–44	44–44	44–45	45–46	46–46	46–46	46–47	46–47	45-45
Incidence rate (per 10^5 persons/year):													
< 35 years	129	127	136	133	129	126	128	127	122	147	158	155	
upper CI limit	124	122	131	128	125	122	123	123	118	142	153	150	
lower CI limit	133	131	140	137	134	131	132	132	127	152	163	160	
35–55 years	256	272	309	333	344	357	358	394	401	519	535	526	
upper CI limit	248	264	300	324	335	347	349	384	392	508	524	515	
lower CI limit	263	280	317	342	353	366	367	404	411	530	546	538	
> 55 years	114	124	154	166	172	195	200	232	243	303	339	322	
upper CI limit	109	118	147	159	165	188	193	224	235	295	330	313	
lower CI limit	120	130	160	172	179	202	207	239	251	312	348	331	
Total	164	170	193	202	205	214	216	235	239	301	320	312	
upper CI limit	160	167	189	198	201	210	212	231	235	296	316	307	
lower CI limit	167	174	197	205	209	217	220	239	243	305	325	316	

CI: 95% confidence intervals.
Annual incidence rates calculated as number of meniscal procedures performed per 100,000 registered Danish inhabitants.

diagnosis coded as "A" (A = action diagnosis, the diagnosis that best describes the condition of a finalized contact) was considered the primary diagnosis. Secondary diagnosis: diagnosis coded as "B" (B = secondary diagnosis, diagnosis that supplements the description of an ended contact).

Incidence rates

Information on numbers of registered inhabitants in Denmark was retrieved from Danish Statistics (www.statistikbanken.dk). As mid-year data was not available, we estimated the mid-year population from numbers at the beginning and the end of each year in the period from 2000 to 2011. These numbers were used to calculate annual incidence rates per 100,000 persons in the age groups: 0–34 years, 35–55 years, and older than 55 years.

Statistics

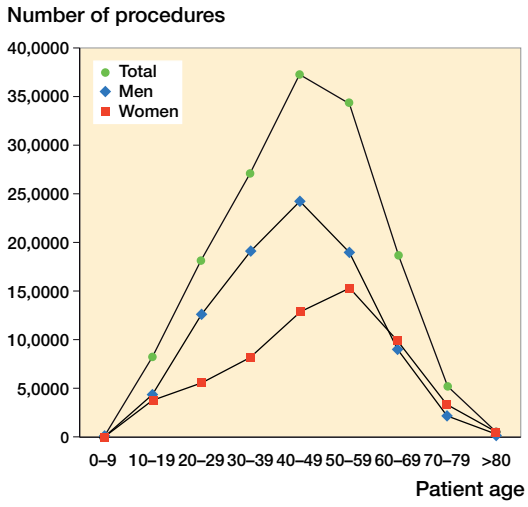
We used chi-square test to assess differences in proportions of meniscal procedures performed on men and women as well as the defined age groups in 2000 as compared to 2011. A 2-sided unpaired Student's t-test, assuming equal variances, was used to assess differences in mean age (with 95% confidence intervals (CIs)) of individuals undergoing meniscal procedures in 2000 as compared to 2011.

Ethics

Data were extracted from the DNPR with approval from Statens Serum Institut (study ID: FSEID 00000526), which is the Danish authority responsible for the DNPR. In addition, the study was approved by the Danish Data Protection Agency (study ID: 2013-41-1792), which must approve all extractions of personal data for research purposes from the DNPR. As the study only pertained to registry-based data, it could be conducted without permission from the Ethics Committee according to Danish legislation (Committee Act § 1, paragraph 1).

Results

The incidence of meniscal procedures per 100,000 persons almost doubled between 2000 and 2011, with a particularly large increase (26%) observed from 2008 to 2009. While the incidence rate was stable in patients younger than 35 years, a doubling was observed for the middle-aged patients between 35 and 55 years of age. For those older than 55, we found a 3-fold increase in incidence rate between 2000 and 2011 (Table 2). This was reflected in a lower proportion of younger patients and a higher proportion of older patients in 2011 compared to 2000 ($p < 0.001$), which also showed in the increase in mean age of patients who underwent meniscal procedures—from 41 (CI: 41–42) in 2000 to 47 (CI: 46–47) in 2011 (Table 2). Middle-aged patients accounted for 50% of the total number of meniscal procedures in the years 2000–2011; the remaining procedures were equally divided between younger (25%) and older patients (25%). Meniscal procedures were carried out in men more frequently than in women (Figure),



Number of meniscal procedures in Denmark (all codes) divided into age groups for the years 2000–2011. Blue: men; red: women; and green: men + women.

but the proportion of women increased from 2000 to 2011 ($p < 0.001$) (Table 2).

The 151,228 meniscal procedures registered between 2000 and 2011 were performed on 148,819 individual patients. Most patients had 1 surgery with 1 meniscal procedure performed, while 1,863 patients had 2 or more meniscal procedures performed at the same operation. Furthermore, 520 patients had more than 1 operation involving procedures to the meniscus within the period 2000–2011. The majority of meniscal procedures (124,363, or 82%) were performed as the primary surgical procedure.

2 NCSP procedure codes accounted for 99% of all 151,228 meniscal procedures. These were KNGD11 (i.e. arthroscopic partial resection of meniscus in knee joint) and KNGD21 (i.e. arthroscopic re-insertion of meniscus in knee joint)—accounting for 92% and 7%, respectively. For those patients with meniscal procedures performed as a secondary surgical procedure (26,865 patients) the most common primary procedures (accounting for 87%) were: anterior cruciate ligament reconstruction (30%: KNGE45*, KNGE51, KNGE55), arthroscopic exploration (28%: KNGA11), synovectomy (18%: KNGF01, KNGF11), and cartilage resection (11%: KNGF31).

Five common diagnoses (i.e. old meniscal tear, traumatic meniscal tear, unspecific knee problems, osteoarthritis, and lesion/rupture of cruciate ligament) represented 80% of all primary diagnoses. Notably, the numbers of diagnoses of "old meniscus tear" and "traumatic meniscus tear" were similar in 2000 (i.e. 2,070 and 2,252, respectively), whereas the diagnosis "old meniscus tear" (n = 5,563) predominated over the diagnosis "traumatic meniscus tear" (n = 3,035) as the primary diagnosis in 2011. Six diagnoses represented 74% of all the secondary diagnoses (Table 3).

Table 3. Most common primary and secondary diagnoses for patients undergoing procedures to the meniscus in the period 2000–2011 in Denmark

	Primary diagnosis	Secondary diagnosis
Old meniscus tear [a]	44,885	9,927
Traumatic meniscus tear [b]	29,163	7,167
Unspecific knee problems [c, d]	28,311	3,277
Osteoarthritis [e, f]	10,860	15,020
Lesion/rupture of cruciate ligament [g, h]	7,999	5,021
Synovitis [i]	–	6,732
Sum of diagnoses above	121,218	47,144
Total number of diagnoses given	151,228	63,618

[a] Primary and secondary diagnosis—old meniscus tear, procedure code DM232.
[b] Primary and secondary diagnosis—traumatic meniscus tear, procedure code DS832.
[c] Primary diagnosis—unspecific knee problems, procedure codes DM23, DM235, DM238, DM239.
[d] Secondary diagnosis—unspecific knee problems, procedure codes DM235, DM238, DM239, DM241.
[e] Primary diagnosis—osteoarthritis, procedure codes DM17, DM170, DM171, DM171A, DM172, DM173, DM175, DM179, DM190, DM199.
[f] Secondary diagnosis—osteoarthritis, procedure codes DM170, DM171, DM171A, DM172, DM173, DM179.
[g] Primary diagnosis—lesion/rupture of cruciate ligament, procedure codes DS835, DS835A, DS835B, DS835E, DS835F.
[h] Secondary diagnosis—lesion/rupture of cruciate ligament, procedure codes DS835, DS835B, DS835E.
[i] Secondary diagnosis—synovitis, procedure codes DM658, DM659, DM659B, DM672, DM673, DM678.

Discussion

The incidence of arthroscopic meniscal procedures in Denmark almost doubled between 2000 and 2011. The largest relative increase in meniscal procedures (i.e. a 3-fold increase in incidence rate) was observed in patients older than 55, whereas the largest absolute increase (i.e. 4,481 procedures) occurred in the middle-aged population between 35 and 55 years of age. In contrast, the incidence rate of meniscal procedures in young patients under 35 was stable. These data suggest that the increased incidence of arthroscopic meniscal surgery mainly involved patients with degenerative meniscal tears, a condition known to be associated with an increased risk of knee osteoarthritis.

Coverage and validity is an important issue for all registries. The validity of registration of orthopedic procedure codes in Denmark has been reported to be good (correct in more than 92% of cases for outpatients), whereas numbers are less precise for diagnosis codes (Lass et al. 2006). It is generally assumed that registration has been complete for public hospitals since 2000, but it is known that reporting is not complete for private hospitals (5% of operations have been estimated to be missing in the DNPR by the Danish National Board of Health) even though this has been mandatory since 2003

(Lynge et al. 2011). In 2005, it was estimated that private payments accounted for around 15% of all healthcare expenses in Denmark (Folketinget 2007). Thus, the numbers in our study may have been underestimated, and some of the changes observed may have been due to variable completeness of reporting. Nevertheless, in comparison to other studies that have reported incidence rates of surgical procedures (Cullen et al. 2009, Abrams et al. 2013), the unique registration of all hospital contacts and concomitantly performed procedures in Denmark, along with the Danish population data, enable reliable estimation of time-related trends in surgical procedures.

Meniscal tears are often associated—by both healthcare professionals and lay-persons—with traumatic sports injuries in young, active individuals (Englund et al. 2012). However, reports from Sweden and the USA show that APM is most often performed in individuals between 45 and 64 years of age (Cullen et al. 2009, Roos and Lohmander 2009, Abrams et al. 2013) Other reports have shown that meniscal tears are also common in asymptomatic knees (Zanetti et al. 2003, Boks et al. 2006, Englund et al. 2007, 2008). Thus, meniscal tears as well as other structural abnormalities characteristic of knee OA (i.e. osteophytes, bone marrow lesions, cartilage damage, etc.) are common incidental findings at MRI examination of both asymptomatic and painful knees of middle-aged and older patients (Englund et al. 2008, Guermazi et al. 2012). Incidental meniscal lesions in these age groups are often of the "degenerative" type and frequently occur in the absence of a distinct trauma but in the presence of other structural joint changes characteristic of knee OA (Englund et al. 2008, 2009).

Taken together, these reports suggest that in the middle-aged and older population, any association between meniscal damage and the development of frequent knee pain exists because both pain and meniscal damage are related to knee OA and not because of a direct link between meniscal tears and pain (Englund et al. 2007, 2008). In our study, only about 17% of those treated with APM had knee OA as the primary or secondary diagnosis. However, the validity of this proportion is limited by the lack of clear diagnostic criteria for OA in the DNPR database, and perhaps also in clinical practice. It is notable that the most frequent primary diagnosis was "old meniscus tear", which commonly occurs in the presence of osteoarthritic joint changes. This primary diagnosis increased 2.7 fold between 2000 and 2011, while the diagnosis of traumatic meniscal tear increased only by a factor of 1.3 in the same time period. Only 1 in 4 of the primary diagnoses were represented by "traumatic meniscus tear" or "anterior cruciate ligament tear".

Consistent with the results from Sweden and the USA (Cullen et al. 2009, Roos and Lohmander 2009), we observed that middle-aged and older individuals accounted for 75% of all meniscal procedures in Denmark between 2000 and 2011. Of the 8,618 additional procedures performed in 2011 compared to 2000, essentially the entire increase was in those aged 35–55 years (4,481 procedures) and in those older than 55 (3,600 procedures). The increasing incidence of APM in the middle-aged and older groups between 2000 and 2011 is surprising, in light of the 3 high-quality randomized controlled trials (RCT) published in the same time period that failed to show any benefit of arthroscopic interventions including APM over and above that of placebo surgery, physiotherapy alone, or physiotherapy in combination with other medical treatments for patients in the same age groups, with or without features of knee osteoarthritis (Moseley et al. 2002, Herrlin et al. 2007, Kirkley et al. 2008) (Table 1). Further consolidating these results, 3 more recent RCTs and an extended follow-up of a previous RCT (Herrlin et al. 2013) showed no additional benefit of APM in combination with physiotherapy compared to physiotherapy alone for patients with meniscal tears and knee osteoarthritis (Katz et al. 2013), no superior effect of APM in comparison to 3 weeks of supervised exercise for middle-aged patients with meniscal tears (Yim et al. 2013), and no difference between APM and placebo surgery in middle-aged patients with meniscal tears and no features of knee OA (Sihvonen et al. 2013) (Table 1). The recent study by Sihvonen et al. (2013) extended previous findings by showing that there was no benefit of APM for middle-aged or older patients with "degenerative" meniscal tears even in the absence of radiographic signs of osteoarthritis. Other studies comparing APM to placebo surgery (Hare et al. 2013) and APM to exercise (ClinicalTrials.gov Identifier: NCT01002794) are under way and may provide further information.

Arthroscopic surgery of the knee is considered to be low-risk surgery. However, the procedures discussed here have been reported to be associated with a 2–3% frequency of adverse events, including deep venous thrombosis, infections, surgical complications, cardiovascular events, pulmonary embolism, and death within 3 months (Noble et al. 1998, Wai et al. 2002, Salzler et al. 2013, Valdes et al. 2013). Some of these adverse events may represent avoidable harm.

In conclusion, a large increase in the incidence of arthroscopic meniscal procedures in middle-aged and older individuals occurred between 2000 and 2011 in Denmark. This increase took place in spite of increasing high-level evidence for a lack of added benefit provided by APM over other treatments in middle-aged and older individuals with and without features of knee OA. Our observations emphasize the long delay in the dissemination, acceptance, and implementation of high-level clinical evidence into the practice of arthroscopic surgery.

JBT and LSL conceived the study. JBT and KBH were responsible for the collection and analysis of data, and all the authors contributed to the interpretation of the data. JBT drafted the manuscript, which was critically revised by KBH and LSL. All the authors approved the final version of the manuscript.

The authors have no competing interests to declare. The study was supported by grants from the Danish Council for Independent Research | Medical Sciences (#12-125457).

Abrams G D, Frank R M, Gupta A K, Harris J D, McCormick F M, Cole B J. Trends in meniscus repair and meniscectomy in the United States, 2005-2011. Am J Sports Med 2013; 41 (10): 2333-9.

Boks S S, Vroegindeweij D, Koes B W, Hunink M M, Bierma-Zeinstra S M. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: Prevalence and associations with tTraumatic history in general practice. Am J Sports Med 2006; 34 (12): 1984-91.

Cullen K A, Hall M J, Golosinskiy A. Ambulatory surgery in the United States, 2006. National Health Statistics Reports, National Center for Health Statistics 2009; 11: 1-28.

Englund M, Niu J, Guermazi A, Roemer F W, Hunter D J, Lynch J A, Lewis C E, Torner J, Nevitt M C, Zhang Y Q, Felson D T. Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. Arthritis Rheum 2007; 56 (12): 4048-54.

Englund M, Guermazi A, Gale D, Hunter D J, Aliabadi P, Clancy M, Felson D T. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008; 359 (11): 1108-15.

Englund M, Guermazi A, Roemer F W, Aliabadi P, Yang M, Lewis C E, Torner J, Nevitt M C, Sack B, Felson D T. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. Arthritis Rheum 2009; 60 (3): 831-9.

Englund M, Roemer F W, Hayashi D, Crema M D, Guermazi A. Meniscus pathology, osteoarthritis and the treatment controversy. Nat Rev Rheumatol 2012; 8 (7): 412-9.

Folketinget EU-Oplysningen (Økonomigruppen og 3. Udvalgssekretariat). Minianalyse: Sundhedssektoren i Danmark: Hvor stor er den, og hvad får vi for pengene? 2007.

Guermazi A, Niu J, Hayashi D, Roemer F W, Englund M, Neogi T, Aliabadi P, McLennan C E, Felson D T. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). BMJ 2012; 345: e5339.

Hare K B, Lohmander L S, Christensen R, Roos E M. Arthroscopic partial meniscectomy in middle-aged patients with mild or no knee osteoarthritis: a protocol for a double-blind, randomized sham-controlled multi-centre trial. BMC Musculoskelet Disord 2013; 14: 71.

Herrlin S, Hallander M, Wange P, Weidenhielm L, Werner S. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. Knee Surg Sports Traumatol Arthrosc 2007; 15 (4): 393-401.

Herrlin S V, Wange P O, Lapidus G, Hallander M, Werner S, Weidenhielm L. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. Knee Surg Sports Traumatol Arthrosc 2013; 21 (2): 358-64.

Katz J N, Brophy R H, Chaisson C E, de Chaves L, Cole B J, Dahm D L, Donnell-Fink L A, Guermazi A, Haas A K, Jones M H, Levy B A, Mandl L A, Martin S D, Marx R G, Miniaci A, Matava M J, Palmisano J, Reinke E K, Richardson B E, Rome B N, Safran-Norton C E, Skoniecki D J, Solomon D H, Smith M V, Spindler K P, Stuart M J, Wright J, Wright R W, Losina E. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med 2013; 368 (18): 1675-84.

Kirkley A, Birmingham T B, Litchfield R B, Giffin J R, Willits K R, Wong C J, Feagan B G, Donner A, Griffin S H, D'Ascanio L M, Pope J E, Fowler P J. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2008; 359 (11): 1097-107.

Lass P, Lilholt J, Thomsen L, Lundbye-Christensen S, Enevoldsen H, Simonsen O H. The quality of diagnosis and procedure coding in Orthopaedic surgery Northern Jutland. Ugeskrift for læger 2006; 168 (48): 4212-5.

Lynge E, Sandegaard J L, Rebolj M. The Danish National Patient Register. Scand J Public Health (7 Suppl) 2011; 39: 30-3.

Moseley J B, O'Malley K, Petersen N J, Menke T J, Brody B A, Kuykendall D H, Hollingsworth J C, Ashton C M, Wray N P. A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee. N Engl J Med 2002; 347 (2): 81-8.

Noble J, Ilango B, Obeid M. Complications of arthroscopy of the knee. The Knee 1998; 5: 1-8.

Pedersen C B. The Danish Civil Registration System. Scand J Public Health (7 Suppl) 2011; 39: 22-5.

Roos E, Lohmander S. Young patients—old knees. Knee problems in the middle age often osteoarthritis. Läkartidningen 2009; 106 (24-25): 1645-8.

Salzler M J, Lin A, Miller C D, Herold S, Irrgang J J, Harner C D. Complications after arthroscopic knee surgery. Am J Sports Med 2013; 42(2): 292-6.

Sihvonen R, Paavola M, Malmivaara A, Itala A, Joukainen A, Nurmi H, Kalske J, Jarvinen T L N. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. New Engl J Med 2013; 369 (26): 2515-24.

Valdes A M, Suokas A K, Doherty S A, Jenkins W, Doherty M. History of knee surgery is associated with higher prevalence of neuropathic pain-like symptoms in patients with severe osteoarthritis of the knee. Semin Arthritis Rheum 2013: [Epub ahead of print]

Wai E K, Kreder H J, Williams J I. Arthroscopic debridement of the knee for osteoarthritis in patients fifty years of age or older: Utilization and outcomes in the province of Ontario. J Bone Joint Surg (Am) 2002; 84 (1): 17-22.

http://www.statistikbanken.dk - accessed Nov 13. Danish Statistics (Danmarks Statistik).

Yim J H, Seon J K, Song E K, Choi J I, Kim M C, Lee K B, Seo H Y. A Comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. Am J Sports Med 2013; 41 (7): 1565-70.

Zanetti M, Pfirrmann C W, Schmid M R, Romero J, Seifert B, Hodler J. Patients with suspected meniscal tears: Prevalence of abnormalities seen on MRI of 100 symptomatic and 100 contralateral asymptomatic knees. AJR Am J Roentgenol 2003; 181 (3): 635-41.

BMJ Open

Large regional differences in incidence of arthroscopic meniscal procedures in the public and private sector in Denmark

Kristoffer Borbjerg Hare,[1,2] Jesper Høeg Vinther,[3] L Stefan Lohmander,[1,4,5] Jonas Bloch Thorlund[1]

To cite: Hare KB, Vinther JH, Lohmander LS, *et al*. Large regional differences in incidence of arthroscopic meniscal procedures in the public and private sector in Denmark. *BMJ Open* 2015;**5**:e006659. doi:10.1136/bmjopen-2014-006659

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2014-006659).

Received 17 September 2014
Revised 15 December 2014
Accepted 13 January 2015

For numbered affiliations see end of article.

Correspondence to
Kristoffer Borbjerg Hare;
kbhr@regionsjaelland.dk

ABSTRACT

Objectives: A recent study reported a large increase in the number of meniscal procedures from 2000 to 2011 in Denmark. We examined the nation-wide distribution of meniscal procedures performed in the private and public sector in Denmark since different incentives may be present and the use of these procedures may differ from region to region.

Setting: We included data on all patients who underwent an arthroscopic meniscal procedure performed in the public or private sector in Denmark.

Participants: Data were retrieved from the Danish National Patient Register on patients who underwent arthroscopic meniscus surgery as a primary or secondary procedure in the years 2000 to 2011. Hospital identification codes enabled linkage of performed procedures to specific hospitals.

Primary and secondary outcome measures: Yearly incidence of meniscal procedures per 100 000 inhabitants was calculated with 95% CIs for public and private procedures for each region.

Results: Incidence of meniscal procedures increased at private and at public hospitals. The private sector accounted for the largest relative and absolute increase, rising from an incidence of 1 in 2000 to 98 in 2011. In 2011, the incidence of meniscal procedures was three times higher in the Capital Region than in Region Zealand.

Conclusions: Our study identified a large increase in the use of meniscal procedures in the public and private sector in Denmark. The increase was particularly conspicuous in the private sector as its proportion of procedures performed increased from 1% to 32%. Substantial regional differences were present in the incidence and trend over time of meniscal procedures.

Strengths and limitations of this study

- Unique nation-wide registration of all hospital contacts and performed procedures in Denmark.
- Reliable estimation of time-related trends in surgical procedures.
- Coverage and validity are an issue for all registry studies.

INTRODUCTION

Arthroscopy for meniscal tears is the most common orthopaedic procedure with at least 700 000 meniscal resections performed in the USA in 2006.[1] A recent study reported a large increase in the number of meniscal procedures from 2000 to 2011 in Denmark.[2] This increase was observed almost exclusively in middle-aged and older patients despite uncertainty of the added benefit provided by arthroscopic partial meniscectomy (APM) over non-surgical treatments on patient-reported knee pain and function in these age groups with or without osteoarthritis (OA).[3–11]

The reason for the large increase in arthroscopic surgery for meniscal tears in Denmark is unclear. Danish media have reported an increase in the number and availability of hospitals and clinics in the private sector since 2005.[12] In the USA, ambulatory surgery centres owned by physicians have surgical rates at least twice as high as outpatient surgery in public hospitals.[13 14] In addition, higher mortality rates and payments have been observed in for-profit hospitals.[15 16] In Denmark, public hospitals are also paid per service provided but the financial incentive for the individual surgeon is likely low as this does not affect individual surgeon salary. Furthermore, large regional differences have been reported in the use of surgical interventions.[17]

To further elucidate the increased use of arthroscopy for meniscal tears in Denmark, we examined the nation-wide distribution of meniscal procedures performed in the private and public sector in Denmark, as different incentives may be present and the use of these procedures may differ from region to region.

PATIENTS AND METHODS

This was a registry study of annual incidences of meniscal procedures in Denmark. We extracted data from The Danish National Patient Register (DNPR). The DNPR registers all patient contacts with hospitals (public and private) in Denmark.[18] Administrative data include the unique person identification number given to all residents in Denmark (Central Person Register—CPR-number[19]), hospital identification, date and time of activity, patient municipality, etc. Clinical data include types of surgical procedures (Nordic Classification of Surgical Procedures (NCSP)) and diagnoses (International Classification of Diseases (ICD-10)). Data were retrieved on all patients who underwent arthroscopic meniscus surgery (KNGD and all subcodes) either as a primary procedure or as part of other surgery in the years 2000 to 2011 (including both years). The CPR-number was used to track patients with several meniscal surgeries (defined as surgery on separate dates) in the study period. In total, 151 228 procedures were performed on 148 819 individual patients.[2] Data were extracted on age and sex together with hospital identification code for each contact, which enables linkage of performed procedures to specific public and private hospitals as well as geographic location. For regional differences, data were obtained from 2005 to 2011. The Regions in Denmark were first established in 2007 in a merger of different municipalities and counties, however, population data are available from 2005.

The DNPR has formed the basis for payment of public healthcare services performed at both public and private hospitals since the year 2000 via the Diagnosis Related Groups (DRG) system in Denmark. It is assumed that registration is complete for these services at public and at private hospitals since 2000. However, for patient paid and private healthcare insurance paid services performed in the private sector, reporting is not complete even though this has been mandatory since 2003. In 2008, it was estimated by the Danish National Board of Health that 5% of all private surgeries were missing in the DNPR.[18] Registration of orthopaedic procedures has been reported to be correct in 92% of a sample of cases (inpatients and outpatients) and is even better for outpatients alone.[20] Arthroscopy codes from public hospitals were recently validated for cartilage injuries of the knee. Registration was correct in 88% of 117 patients.[21]

Denmark is divided into five regions: The Capital Region, Region Zealand, Region of Southern Denmark, Region Mid and Region North. Information on numbers of registered inhabitants of all ages in each region, per 1 January, for each year in the period from 2005 to 2012, was retrieved from Danish Statistics (http://www.statistikbanken.dk—accessed 13 March). Mid-year population was estimated from numbers at the beginning and end of each year. Yearly incidence of arthroscopic meniscal procedures per 100 000 inhabitants (all ages) was calculated with 95% CI for procedures performed in the public and private sector, respectively, for each region.

The χ^2 test was used to assess differences in proportions of meniscal procedures performed on middle-aged and older patients, defined as aged 35 years and older, in the public sector compared with the private sector.

ETHICS

Data were extracted from the DNPR with approval from Statens Serum Institut (study ID: FSEID 00000526), which is the Danish authority responsible for the DNPR. In addition, the study was approved by the Danish Data Protection Agency (study ID: 2013-41-1792), which must approve all extractions of personal data for research purposes from the DNPR. As the present study only pertains to register-based data it can be conducted without permission from the Ethics Committee according to Danish legislation (Committee Act § 1, paragraph 1).

RESULTS

Incidence of meniscal procedures increased at private and at public hospitals. However, the proportion of procedures performed in the private sector increased from 1% in 2000 to 32% in 2011 (figure 1) and the private sector also accounted for the largest increase in total number of procedures, rising from 65 procedures in 2000 to 5478 in 2011. Still, the majority of meniscal procedures in Denmark are carried out in the public sector. In the same time interval, the number of private hospitals and clinics reporting to the DNPR in Denmark more than tripled from 16 in 2000 to 52 in 2011, with the largest increase observed in the Capital Region (from 7 to 24). Yearly incidence of arthroscopic meniscal procedures for the private sector in Denmark increased from 1 (95% CI 0.9 to 1.5) in 2000 to 98 (96 to 101) in 2011. The increase in incidence in the public sector in the same time period rose from 163 (159 to 166) to 213 (210 to 217). There was a significant difference ($p<0.001$) in age distribution as the private sector performed 83% of the procedures in patients aged 35 years and older compared to 73% in the public sector (table 1).

Large regional differences were present (table 2). In 2011, the total incidence (public and private) in the Capital Region was three times higher than in Region Zealand. The largest increase in incidence between 2005 and 2011 occurred in the Capital Region, from 165 (159–171) to 366 (357–375), while in two regions, Zealand and North, the incidence remained stable between 2005 and 2011.

Incidence of meniscal procedures in the private sector increased in all regions. In Region Mid the overall increase was exclusively caused by an increase in incidence of procedures performed in the private sector while the incidence of procedures increased in the public as well as private sector in the Capital Region and in Region of Southern Denmark. In Region North, the

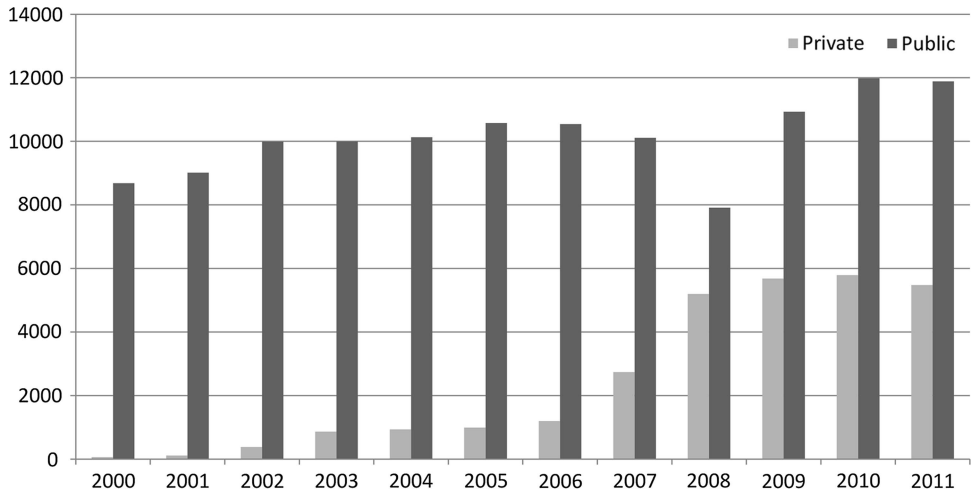


Figure 1 Total number of meniscal procedures divided between public and private hospitals/clinics from 2000 to 2011 in Denmark.

incidence at private hospitals increased while the incidence rate decreased at public hospitals. In 2011 more meniscal procedures were performed in the private sector than in the public sector in the Capital Region while the public sector still accounted for most procedures performed in all other regions.

DISCUSSION

Key results

We examined the distribution of public and private sector meniscal procedures performed in Denmark together with regional differences. Incidence of meniscal procedures rose in the public and in the private sectors but the proportion of procedures performed in the private sector increased from 1% to 32% over the 12-year period. In the same time period, the incidence of meniscal procedures performed in the public sector increased by 31%. The proportion of procedures performed in patients aged 35 years and older was larger in the private sector: 83% compared to 73% in the public sector. While the incidence was stable in two regions (Zealand and North), it increased markedly in the public as well as the private sector in the Capital Region and in the Region of Southern Denmark. In Region Mid the increase in incidence of procedures was observed exclusively in the private sector.

Interpretation

There may be several reasons for the increase in incidence of meniscal procedures performed in the public and private healthcare sectors in Denmark. The most obvious would be an increased incidence of meniscal tears, which could be caused by increased sports and exercise participation in the adult population. In Denmark, the proportion of adults who self-reported participation in sport and exercise increased from 50% to 64% from 1998 to 2011. The predominant activities reported were jogging (31% of adult population), strength training (24%) and hiking (23%),[22] none of these is recognised as a high risk activity for meniscal injury.[23] Even though increased participation in sports and exercise may not lead to direct injury, it may contribute to symptom onset in patients with latent

Table 1 Number of meniscal procedures distributed by age and public or private sector

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
>55 years													
Public	1478	1640	2023	2104	2228	2585	2630	2772	2268	3236	3834	3779	30 577
Private	32	35	98	231	240	261	336	710	1435	1446	1467	1331	7622
35–55 years													
Public	4129	4382	4853	4974	5037	5241	5117	4830	3688	5196	5364	5275	58 086
Private	26	58	185	434	530	524	675	1569	2859	3297	3401	3361	16 919
<35 years													
Public	3078	2994	3111	2921	2867	2751	2798	2508	1957	2499	2783	2836	33 103
Private	7	26	99	203	169	212	189	463	903	941	923	786	4921
Total													
Public	8685	9016	9987	9999	10 132	10 577	10 545	10 110	7913	10 931	11 981	11 890	121 766
Private	65	119	382	868	939	997	1200	2742	5197	5684	5791	5478	29 462

Table 2 Number and incidence rates of meniscus procedures in the different regions in Denmark

	2005	2006	2007	2008	2009	2010	2011
Total							
Public, n	10 577	10 545	10 110	7913	10 931	11 981	11 890
Private, n [%]	997 [9]	1200 [10]	2742 [21]	5197 [40]	5684 [34]	5791 [33]	5478 [32]
Public incidence	195 (191 to 199)	194 (190 to 198)	185 (182 to 189)	144 (141 to 147)	198 (194 to 202)	216 (212 to 220)	213 (210 to 217)
Private incidence	18 (17 to 20)	22 (21 to 23)	50 (48 to 52)	95 (92 to 97)	103 (100 to 106)	104 (102 to 107)	98 (96 to 101)
Region capital							
Public, n	2370	2357	2230	1767	2565	3366	3084
Private, n [%]	325 [12]	380 [14]	866 [28]	1760 [50]	1948 [43]	2152 [39	3167 [51]
Public incidence	145 (139 to 151)	144 (138 to 150)	136 (130 to 142)	107 (102 to 112)	153 (148 to 159)	199 (192 to 206)	181 (174 to 187)
Private incidence	20 (18 to 22)	23 (21 to 26)	53 (49 to 56)	106 (101 to 111)	117 (111 to 122)	127 (122 to 133)	186 (179 to 192)
Region Zealand							
Public, n	1013	999	879	717	883	913	792
Private, n [%]	46 [4]	37 [4]	91 [9]	176 [20]	252 [22]	332 [27]	221 [22]
Public incidence	125 (118 to 133)	123 (115 to 130)	107 (100 to 115)	87 (81 to 94)	108 (100 to 115)	111 (104 to 119)	97 (90 to 103)
Private incidence	6 (4 to 7)	5 (3 to 6)	11 (9 to 13)	21 (18 to 25)	31 (27 to 34)	40 (36 to 45)	27 (23 to 31)
Region South							
Public, n	2576	2601	2355	1769	2999	3072	3429
Private, n [%]	339 [12]	443 [15]	677 [22	1204 [40]	1020 [25]	965 [24]	811 [19]
Public incidence	217 (209 to 226)	219 (211 to 227)	198 (190 to 205)	148 (141 to 155)	250 (241 to 259)	256 (247 to 265)	286 (276 to 295)
Private incidence	29 (26 to 32)	37 (34 to 41)	57 (53 to 61)	101 (95 to 106)	85 (80 to 90)	80 (75 to 85)	68 (63 to 72)
Region Mid							
Public, n	3389	3464	3692	3066	3607	3751	3449
Private, n [%]	177 [5]	207 [6]	487 [12]	823 [21]	1545 [30]	1486 [28]	1003 [23]
Public incidence	279 (269 to 288)	283 (274 to 296)	300 (290 to 309)	247 (238 to 256)	288 (279 to 298)	298 (289 to 308)	273 (264 to 282)
Private incidence	15 (12 to 17)	17 (15 to 19)	40 (36 to 43)	66 (62 to 71)	124 (117 to 130)	118 (112 to 124)	79 (74 to 84)
Region North							
Public, n	1229	1124	954	594	877	879	1136
Private, n [%]	110 [8]	133 [11]	621 [39]	1234 [68]	919 [51]	856 [49]	276 [20]
Public incidence	213 (201 to 225)	195 (183 to 206)	165 (155 to 176)	102 (94 to 111)	151 (141 to 161)	152 (142 to 162)	196 (185 to 207)
Private incidence	19 (16 to 23)	23 (19 to 27)	107 (99 to 116)	213 (201 to 225)	158 (148 to 169)	148 (138 to 158)	48 (42 to 53)

Numbers in brackets are 95% CI.
N, number of procedures.

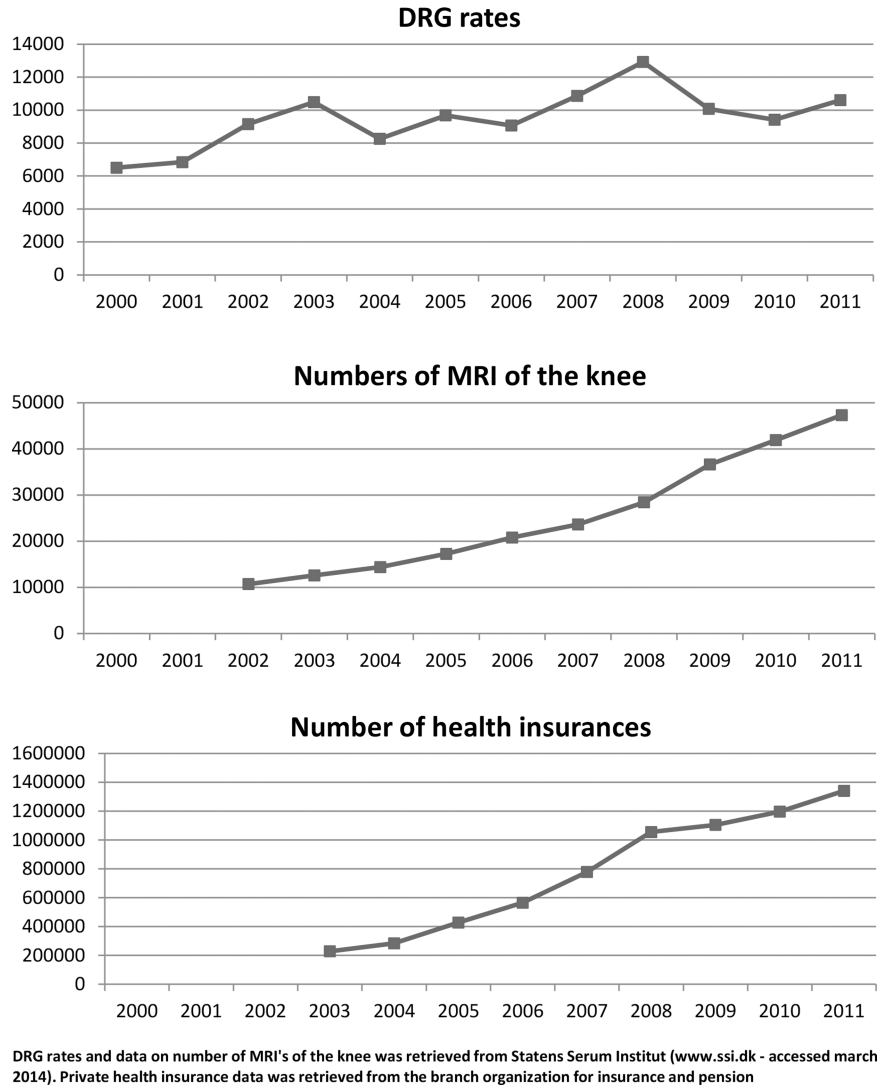


Figure 2 Trends of Diagnosis Related Groups (DRG) rate (2000–2011), use of knee MRI examinations (2002–2011) and private health insurances (2003–2011).

degenerative knee disease such as degenerative meniscal tears. Thus, increased participation in sport and exercise may have caused an increased incidence on patient demand of care (ie, meniscal surgery) but is unlikely to be responsible for the large increase observed.

Another plausible reason includes financial reimbursement. In Denmark, the public sector and to some extent the private sector is paid according to the DRG rate. DRG is a classification system for patients originally developed in the USA but modified to fit the Danish diagnosis and treatment definitions.[24] DRG rates represent prices for treatments within each group based on estimated average costs. This system was introduced in 1 January 2000. The DRG rate for arthroscopic knee surgery increased from 6502 DKK in 2000 to 10 483 in 2003 and was relatively stable thereafter (figure 2). Payment per procedure provides a potential incentive for surgeons to provide more procedures because payment is dependent on the quantity of care rather than the quality and outcome of care. Indeed, financial reimbursement has been shown to influence surgical decision-making in the private sector because of greater financial incentives for surgeons.[13 14] To the best of our knowledge, whether this could also be the case in the public sector, where the financial incentive lies within the department and not the individual surgeon, has not been investigated. Still, a concern remains that surgery in this context may be preferred when watchful waiting and/or physiotherapy is the other, less profitable alternative.[18]

Another potential cause is the political introduction of the 'extended free hospital choice', also known as the 'treatment guarantee', introduced in Denmark on 1 July 2002. The treatment guarantee allows patients to be treated at another public hospital or in the private sector if the initially chosen public hospital is not able to offer treatment within 2 months. This likely led to an increase in incidence of meniscal procedures performed in the private sector as well as in number of private hospitals and clinics in the period 2000 to 2011. The increase in incidence of meniscal procedures was further enhanced when the treatment guarantee was reduced to 1 month on 1 October 2007. In the public sector, there was a decline in incidence of meniscal

procedures performed between 2006 and 2008, while in the same time period, a large increase in incidence of procedures was observed in the private sector (figure 1). This could represent patients 'shifting' from the public to the private sector as a consequence of the treatment guarantee in combination with a nurses strike in the public sector from April to June 2008.

The proportion of the Danish population having private health insurance increased from 4% in 2003 to 24% in 2011 (figure 2). This likely facilitated access to surgery for those with private health insurance and may have contributed to the shifting of patients from the public to the private sector. Providing quick treatment for patients is often considered beneficial for early recovery and prognosis. However, in conditions where symptoms are known to fluctuate, such as in knee OA, quick access to surgery may actually not be advantageous since symptoms could remit without surgery. Indeed, for middle-aged and older patients, meniscal surgery is most often a resection of a degenerative meniscal tear.[2] The knee symptoms of these patients are likely related to degenerative knee disease rather than meniscal tear,[25] and it is recommended that the disease be treated according to clinical guidelines of knee OA with patient education, physiotherapy and weight loss if needed.[26]

MRI examinations of the knee are increasingly used in diagnosing meniscal pathology and could influence surgical decision-making by detecting previously undiagnosed meniscus tears in a painful knee. Meniscal tears visualised on MRI provide a persuasive indication for surgery for the surgeon and for the patient with a painful knee. Indeed, the use of MRI of the knee has increased fivefold between 2002 and 2011 (figure 2). However, positive findings on MRI are common also in asymptomatic individuals and even more common in knees with OA.[27 28] The increased use of MRI as a diagnostic tool could lead to treatment of patients whose symptoms are not related to a meniscal lesion, but to knee OA.

Even though financial incentives and the treatment guarantee seem plausible causes for the increased incidence of meniscal procedures, these causes are unlikely to account for the regional variations since regions share the same national reimbursement and healthcare policy. In the present study, we found large differences in incidence of meniscal procedures between regions, with the lowest incidence being 124/100 000 (116–131) in Region Zealand in 2011, compared to a three times greater incidence rate of 366 (357–375) in 2011 in the Capital Region. Large regional variations may suggest variations in surgeons' opinions about clinical indications for surgery. This is known for indications of knee arthroplasty.[29] However, a systematic review showed little evidence of different beliefs in clinical indications as a cause of regional variations in use of coronary angiography, upper gastrointestinal endoscopy and carotid endarterectomy.[30] If different clinical indications are not the cause of regional variation then high surgical rates in some regions may be related to traditions in surgical training or a strong belief in a specific procedure.[31 32] In this study, we found a low incidence of meniscal surgery in Region North but a report on shoulder surgery in Denmark found a high incidence of shoulder arthroscopy in the same region compared to the other regions.[33] It seems there is little correlation in regional rates of procedures even within the same specialty. Similar discrepancies have been found in the USA.[17]

Patient willingness to undergo surgery could be another cause of regional variation and has been reported to be higher in areas with higher incidence for knee arthroplasty.[34] There may also be differences in the patient information given and in the willingness to incorporate the patients in the decision-making process of having surgery. These variations are also known to influence surgical rates.[35 36]

Limitations

There are some limitations associated with our study. The DNPR does not differentiate between the regions patients reside in. It is possible that some patients received surgery in a Region other than their residential region. For instance, Region Zealand is closely related to the Capital Region and some patients may have chosen to be operated in a private hospital in the Capital Region. We assumed that registration in the DNPR has been complete for public hospitals since 2000. However, for private hospitals and clinics, reporting is not complete even though this has been mandatory since 2003. The Danish National Board of Health estimated that 5% of all private surgeries were missing in the DNPR.[18] Thus, numbers of procedures in the private sector may be underestimated in the present study and some of the changes observed may be due to variable completeness of reporting.

Conclusions

A large increase in the use of meniscal procedures at public and at private hospitals in Denmark was observed between 2000 and 2011. The increase was particularly conspicuous in the private sector, as the proportion of procedures performed increased from 1% to 32% over the investigated 12-year period. Potential causes for the observed increase include financial reimbursement and healthcare policies along with an increase in number of private health insurances and MRI examinations of the knee. Substantial regional differences were present in the utilisation rate and trend over time of meniscal procedures. The exact reasons for this remain unknown. The increasing use and regional variation of meniscal procedures in the middle-aged and elderly is notable given the uncertainty for added patient-centred benefit from the intervention.

Author affiliations
[1]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
[2]Department of Orthopedics, Slagelse Hospital, Region Zealand, Denmark

[3]Department of Orthopedics, Kolding Hospital, Region of Southern Denmark, Denmark
[4]Department of Orthopedics, Clinical Sciences Lund, University of Lund, Sweden
[5]Department of Orthopedics and Traumatology, Odense University Hospital, Denmark

Contributors LSL and JBT conceived the study. KBH, JHV and JBT were responsible for the collection and analysis of data and all authors contributed to the interpretation of the data. KBH drafted the manuscript, which was critically revised by JHV, JBT and LSL. All authors approved the final version of the manuscript.

Funding The study was supported by grants from The Danish Council for Independent Research | Medical Sciences (#12-125457).

Competing interests None.

Ethics approval Danish Data Protection Agency (study ID: 2013-41-1792).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.fq268.

REFERENCES

1. Cullen K, Hall M, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report* 2009;(11):1–25.
2. Thorlund JB, Hare KB, Lohmander LS. Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011. *Acta Orthop* 2014;85:287–92.
3. Herrlin S, Hållander M, Wange P, *et al*. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. *Knee Surg Sports Traumatol Arthrosc* 2007;15:393–401.
4. Herrlin SV, Wange PO, Lapidus G, *et al*. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. *Knee Surg Sports Traumatol Arthrosc* 2013;21:358–64.
5. Moseley JB, O'Malley K, Petersen NJ, *et al*. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81–8.
6. Kirkley A, Birmingham TB, Litchfield RB, *et al*. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2008;359:1097–107.
7. Yim JH, Seon JK, Song EK, *et al*. A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. *Am J Sports Med* 2013;41:1565–70.
8. Sihvonen R, Paavola M, Malmivaara A, *et al*. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515–24.
9. Katz JN, Brophy RH, Chaisson CE, *et al*. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med* 2013;368:1675–84.
10. Gauffin H, Tagesson S, Meunier A, *et al*. Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study. *Osteoarthritis Cartilage* 2014;22:1808–16.
11. Khan M, Evaniew N, Bedi A, *et al*. Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *CMAJ* 2014;186:1057–64.
12. Møller KP. Eksplosiv stigning i omstridte operationer. *Altinget* 2010.
13. Hollingsworth JM, Ye Z, Strope SA, *et al*. Physician-ownership of ambulatory surgery centers linked to higher volume of surgeries. *Health Aff* 2010;29:683–9.
14. Mitchell JM. Effect of physician ownership of specialty hospitals and ambulatory surgery centers on frequency of use of outpatient orthopedic surgery. *Arch Surg* 2010;145:732–8.
15. Devereaux PJ, Heels-Ansdell D, Lacchetti C, *et al*. Payments for care at private for-profit and private not-for-profit hospitals: a systematic review and meta-analysis. *CMAJ* 2004;170:1817–24.
16. Devereaux PJ, Choi PT, Lacchetti C, *et al*. A systematic review and meta-analysis of studies comparing mortality rates of private for-profit and private not-for-profit hospitals. *CMAJ* 2002;166:1399–406.
17. Birkmeyer JD, Reames BN, McCulloch P, *et al*. Understanding of regional variation in the use of surgery. *Lancet* 2013;382: 1121–9.
18. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30–3.
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(7 Suppl):22–5.
20. Lass P, Lilholt J, Thomsen L, *et al*. Kvaliteten af diagnose- og procedurekodning i Ortopædkirurgi Nordjylland. *Ugeskr Læger* 2006;168:4212–15.
21. Mor A, Grijota M, Norgaard M, *et al*. Trends in arthroscopy-documented cartilage injuries of the knee and repair procedures among 15–60-year-old patients. *Scand J Med Sci Sports* 2014.
22. Laub TB, Pilgaard M. *Sports participation in Denmark 2011*. Danish Institute for Sports Studies, 2013.
23. Snoeker BA, Bakker EW, Kegel CA, *et al*. Risk factors for meniscal tears: a systematic review including meta-analysis. *J Orthop Sports Phys Ther* 2013;43:352–67.
24. Vrangbæk K, Bech M. County level responses to the introduction of DRG rates for "extended choice" hospital patients in Denmark. *Health Policy* 2004;67:25–37.
25. Englund M, Roemer FW, Hayashi D, *et al*. Meniscus pathology, osteoarthritis and the treatment controversy. *Nat Rev Rheumatol* 2012;8:412–19.
26. Fernandes L, Hagen KB, Bijlsma JWJ, *et al*. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–35.
27. Guermazi A, Niu J, Hayashi D, *et al*. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ* 2012;29:e5339.
28. Englund M, Guermazi A, Gale D, *et al*. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108–15.
29. Troelsen A, Schroder H, Husted H. Opinions among Danish knee surgeons about indications to perform total knee replacement showed considerable variation. *Dan Med J* 2012;59:A4490.
30. Keyhani S, Falk R, Bishop T, *et al*. The relationship between geographic variations and overuse of healthcare services: a systematic review. *Med Care* 2012;50:257–61.
31. Chassin MR. Explaining geographic variations. The enthusiasm hypothesis. *Med Care* 1993;31(5 Suppl):37–44.
32. Bederman SS, Coyte PC, Kreder HJ, *et al*. Who's in the driver's seat? The influence of patient and physician enthusiasm on regional variation in degenerative lumbar spinal surgery: a population-based study. *Spine* 2011;36:481–9.
33. Løvschall C, Witt F, Svendsen S, *et al*. Medicinsk teknologivurdering af kirurgisk behandling af patienter med udvalgte og hyppige skulderlidelser. Århus: MTV og Sundhedstjenesteforskning, Region Midtjylland. 2011.
34. Hawker G, Wright JG, Coyte PC, *et al*. Determining the need for hip and knee arthroplasty: the role of clinical severity and patients' preferences. *Med Care* 2001;39:206–16.
35. Arterburn D, Wellman R, Westbrook E, *et al*. Introducing decision aids at Group Health was linked to sharply lower hip and knee surgery rates and costs. *Health Aff* 2012;31:2094–104.
36. McCulloch P, Nagendran M, Campbell WB, *et al*. Strategies to reduce variation in the use of surgery. *Lancet* 2013;382:1130–9.

Submitted March 2015 to Knee Surgery, Sports Traumatology, Arthroscopy.

Self-reported knee symptoms in 199 middle-aged patients with an MRI-verified medial meniscal tear eligible for arthroscopic partial meniscectomy: a cross sectional study.

Kristoffer B Hare[1,2], L Stefan Lohmander[1,3,4], Nina Jullum Kise[5], May Arna Risberg[6], Ewa M Roos[1]

Address

[1]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Denmark

[2]Department of Orthopedics, Slagelse Hospital, Region Zealand, Denmark

[3]Department of Orthopedics, Clinical Sciences Lund, University of Lund, Sweden

[4]Department of Orthopedics and Traumatology, Odense University Hospital, Denmark

[5]Department of Orthopedics, Martina Hansens Hospital, Norway

[6]Norwegian Research Center for Active Rehabilitation, Department of Orthopedic Surgery, Oslo University Hospital, and Department of Sports Medicine, Norwegian School Sport Sciences, Norway

*Corresponding Author, email: kbhr@regionsjaelland.dk, phone: +45 29 25 69 74

Level of evidence: IV

Keywords: Meniscus, surgery, symptoms, knee, osteoarthritis, middle-aged.

Abstract

Purpose

To determine prevalence and severity of self-reported knee symptoms in patients eligible for arthroscopic partial meniscectomy. To investigate if early radiographic signs of knee osteoarthritis were associated with self-reported knee symptoms.

Methods

We included individual baseline items from the Knee injury and Osteoarthritis Outcome Score (KOOS) collected in two ongoing randomized controlled trials evaluating treatment for degenerative medial meniscus tears in patients 35–65 years old with an MRI verified medial meniscus tear. Each item was scored as no, mild, moderate, severe, extreme, and at least 'mild' was required for the symptom to be considered present. Early radiographic signs of osteoarthritis were defined as a Kellgren and Lawrence score of at least 1.

Results

Monthly knee pain, knee pain during certain activities and lack of confidence in knee was present in at least 80% of the patients. Median severity was at least moderate for knee pain, knee pain during certain activities, lack of confidence in knee and clicking. Mechanical symptoms as catching were rare. Early radiographic signs of osteoarthritis were associated with an increased risk of self-reported swelling, catching and stiffness later in day; odds ratio 2.4 (1.2-4.9, 95% CI), 2.3 (1.2-4.3) and 2.3 (1.1-5.0), respectively.

Conclusion

Middle-aged patients with a degenerative medial meniscus tear reported symptoms commonly associated with knee osteoarthritis. Meniscus patients reporting swelling of the knee, stiffness later in day or catching were at higher risk of radiographic signs of osteoarthritis. Our findings support that symptoms reported by those with a degenerative meniscal tear represent early signs of knee osteoarthritis.

Introduction

Background

MRI-verified meniscus tears are common in the population [1] and arthroscopic partial meniscectomy (APM) is the most commonly performed orthopedic procedure, carried out in at least half a million patients annually in the USA [2, 3]. No consensus exists on when APM is indicated [4] and uncertainty exists of added benefit of APM compared to non-surgical interventions [5-10]. Further, the diagnostic criteria of a meniscus tear are not consistently defined and provision varies widely even within regions of a single country [11, 12]. Magnetic Resonance Imaging (MRI) is increasingly used as a diagnostic tool. MRI can identify meniscus tears in symptomatic patients [13], but also detects asymptomatic meniscus tears in the general population [1]. Even in the presence of a meniscus tear on MRI, coexisting knee osteoarthritis (OA) may be the primary cause of knee pain and symptoms [14]. Thus, an MRI-verified tear in the presence of knee pain does not provide an indication for APM. To identify if the symptoms origin from the meniscus tear the physician relies on clinical tests. These tests have not proven to be very accurate and repeat studies suggest that no single test can definitively diagnose symptomatic meniscus tears [15-19].

Symptoms commonly considered related to meniscus injury include knee pain, giving way and mechanical symptoms like clicking, locking or catching, and there is some evidence for their validity in identifying symptomatic meniscus tears when ascertained by the clinician [20-22]. Self-reported questionnaires are another way to obtain patient history. Patient-reported outcomes (PROs) are used to determine the patient's perception of a disease, and the outcome from an intervention, but PROs are rarely used as diagnostic tools [23]. This approach may however be appealing since PROs are less prone than clinical history taking to interviewer bias [24-27].

The aim of this study was firstly to determine the prevalence and severity of commonly assessed self-reported knee symptoms, including knee pain, clicking, catching and giving way, by the use of a patient-administered questionnaire in middle-aged patients eligible for arthroscopic partial meniscectomy. Secondly, to investigate if

occurrence of concomitant early radiographic signs of knee OA were associated with self-reported knee symptoms.

Methods

We used a cross-sectional design and included baseline data collected in two different randomized controlled trials evaluating treatment of degenerative medial meniscus tears, the OMEX and the SLAMSHAM studies (ClinicalTrials.gov Identifier: NCT01002794 and NCT01264991) [28-31]. The trials compared arthroscopic partial meniscectomy with exercise therapy or sham surgery, respectively. Patient characteristics, mean Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale scores and functional outcomes determined at baseline are published for the first 82 patients included in the OMEX study [30, 31]. Data on individual items from the KOOS are previously unpublished.

Participants were between 35 and 65 years old with an MRI verified degenerative medial meniscus tears, at least 2 months duration of knee pain and no previous significant trauma, found eligible for arthroscopic partial meniscectomy. Only patients with no or mild knee osteoarthritis (OA), Kellgren and Lawrence grade 0-2 [32, 33] were included. Eligibility for surgery was based on clinical examination by an orthopedic surgeon and the presence of a degenerative meniscus tear on MRI. An increased intra-meniscus signal (commonly a linear signal within the meniscus) was regarded as a meniscus tear when it communicated with the inferior or superior margin of the meniscus on at least two consecutive slices from the MRI investigation.

Patients were recruited through outpatient orthopedic clinics in Norway or Denmark between 2009 and 2013. In the OMEX study the sample size for the RCT determined the current study sample (n=140). In the SLAMSHAM study, recruitment is still ongoing and study sample was determined by patients included in the RCT (n=40) and by patients meeting all the inclusion criteria but declined participation enrolled in a parallel cohort study (n=19).

Assessments

Knee injury and Osteoarthritis Outcome Score (KOOS)

We used the KOOS to collect patient-reported knee symptoms [34]. The KOOS is a 42-item self-administered knee-specific questionnaire assessing pain (9 items), symptoms (7 items), activities of daily living (17 items), sport and recreation function (5 items) and knee-related quality of life (4 items) in five separate subscales. KOOS is validated for short- and long-term follow-up studies of knee injury and OA [34-36]. KOOS questionnaires were filled out by the patients prior to randomization without the help of an interviewer. In the current study, we included all individual items from the subscales pain (7 items) and symptoms (9 items) and one item from subscale quality of life. These 17 items were selected since they represent clinical symptoms commonly thought to be associated with a meniscal tear [20-22] (**Table 1**). Each item in KOOS is responded to by marking one of five response options on a Likert scale. For each individual item, presence of a symptom was defined as reporting at least mild symptoms; ticking the second to fifth out of the five Likert boxes representing no, mild, moderate, severe or extreme symptoms, or equivalent.

Radiographic scoring of the knee joint

The Kellgren and Lawrence (K&L) score was used to assess structural disease severity. A preoperative posterior-anterior radiograph of both knees with a fixed-flexion radiography procedure, with use of SynaFlexer™ [37], was performed. This provides radiography at the exact same position and is validated in determining joint space width (JSW) in knee osteoarthritis [38]. No radiograph of the patellofemoral joint was performed. Radiographs were assessed by an orthopedic surgeon when assessing patients for eligibility. A K&L grade of zero would imply no structural changes, a K&L grade of 1 a minute osteophyte of doubtful significance, and a K&L grade of 2 a definite osteophyte with unimpaired joint space [32, 39]. Presence of early radiographic knee OA was defined as a K&L score of 1 or 2 [40-42].

Statistical analysis

The prevalence of knee symptoms is given as the percentage with 95 % confidence intervals (95 % CI) and defined as patients reporting at least mild problems. Symptom severity is given as the median with interquartile

range (IQR) for the severity grade (range, 0-4 (no, mild, moderate, severe, extreme or equivalent)) for each of the reported symptoms.

We used logistic regression to evaluate the association between concomitant structural disease and presence of a symptom while adjusting for age, gender and BMI. Odds ratio, 95% CI and p-values are given for all regression analyses.

Results

We included 199 patients in this study (**Table 2**). Average age was 48 years and 41 % were women. Sixty-five percent of the patients had no concomitant structural disease on radiography (K&L = 0).

The four most commonly reported symptoms were frequent knee pain, lack of confidence in knee, pain when pivoting/twisting and pain when walking up or down stairs. These four symptoms were reported by more than 80 percent of the patients (**Figure 1**). The least commonly reported symptoms were catching and difficulty straightening knee fully, reported by less than 40% of the patients. All other symptoms were reported by 50-80% of the patients.

The median frequency for knee pain was 'daily', on a scale ranging from never, monthly, weekly and daily to always. The median severity was 'moderate' on a scale from no problems, mild, moderate, and severe to extreme for lack of confidence in knee, clicking, pain when pivoting/twisting, pain when walking up or down stairs and pain when bending knee fully. The median for the two items with lowest severity, catching and difficulty straightening knee fully, was 'no problems'. For the remaining 9 items, the median severity was 'mild'.

The adjusted analysis for the association of early radiographic knee OA with presence of each of the 17 symptoms indicated that early structural disease (grade 1 or 2 on the K&L scale) was associated with a higher risk of self-reported swelling, catching and stiffness later in the day (**Table 3**).

Discussion

Key Results

In this cross-sectional study of middle-aged patients eligible for APM we aimed to determine the prevalence and severity of self-reported knee symptoms and the association of early radiographic knee OA with presence of these symptoms. We showed a prevalence of more than 80% and at least a moderate severity of the self-reported symptoms knee pain, lack of confidence, pain when pivoting/twisting and pain walking up/down stairs. Mechanical symptoms as catching and difficulty straightening knee were neither frequent nor severe. Early radiographic signs of knee OA were associated with higher risk of swelling, catching and stiffness later in day.

Limitations

There are some limitations to our study. The cross-sectional design of our study did not allow for analysis of predictors of the outcome or causality. In addition, diagnostic sensitivity and specificity could not be determined since we had no 'control group' i.e. patients considered eligible by the surgeon but who failed to demonstrate a meniscus lesion on MRI. Another limitation is the use of RCT baseline data for a cohort study. Randomized trials have strict inclusion and exclusion criteria, and despite being set to optimize external validity, included patients are more selected than if data from the full population having meniscus surgery had been included.

We defined early radiographic signs of knee OA as Kellgren and Lawrence grade ≥1. Commonly, a cut-off point of 2 on the K&L scale is used for radiographic knee OA [32]. However, several studies have shown a strong association between the presence of osteophytes on radiography and the presence of self-reported symptomatic knee OA confirmed by MRI or arthroscopic visualization [40]. Therefore, we used K&L grade 1 as the cut-off point for concomitant radiographic signs of early knee OA.

Interpretation

Prevalence of symptoms

A recent study examined the reliability and validity of the clinical history relevant to meniscus tear [20]. As a result, a Meniscal Symptom Index (MSI) consisting of four symptoms (localized pain, clicking, catching, and giving way) was identified to help standardize the clinical history ascertained by the clinician and eligibility for arthroscopic partial meniscectomy. The four symptoms included in the MSI were all to a varying degree present in our population.

Knee pain was present in all patients and had the greatest severity of all symptoms. This was expected since knee pain was one of the inclusion criteria for the RCTs from where our data were collected and is the most common symptom leading to APM [4, 43]. The self-reported prevalence and severity of lack of confidence in the knee was also high. 'Lack of confidence' is related to but not identical with 'giving way' which is the wording used in the MSI. Asking the patients about confidence in their knee is closely related to the extent to which the patient is actually troubled by their knee giving way as opposed to experiencing an actual giving way episode. Clicking is often thought to be a sound emanating from the meniscus subluxating from its place in the knee joint. However, clicking was not more common or severe than other self-reported symptoms.

Catching was the least reported symptom of all. This finding may seem surprising since catching is almost universally considered an absolute indication for surgery [4]. Other authors also reported a low incidence of catching/locking in cohorts defined by having meniscal tears [20-22]. Studies have shown that patients with catching may get better without surgery [8] and in two recent studies of arthroscopic partial meniscectomy patients reporting catching or locking symptoms did not gain more effect from APM than those without [5, 10]. Therefore, even though catching or locking is generally acknowledged as an indication for meniscal surgery the evidence for its relation to a meniscus tear or an added benefit from partial meniscectomy is scanty.

We found two symptoms not included in the MSI, which were of high self-reported frequency and severity: pain when pivoting/twisting and pain going up/down stairs. Niu et al. also reported a high incidence of pain on pivoting/twisting but this item was excluded from the MSI due to a low positive predictive value indicating that

other knee conditions were more likely to produce this symptom. Pain going up/down stairs has not been previously described as a prevalent symptom in those with a meniscus tear and is thought to be more common in those with patellofemoral osteoarthritis [44]. Radiography of the patellofemoral joint was not performed in our study to evaluate this possibility. It seems however, that pain going up or down stairs is common also in cohorts defined by having structural damage in the tibiofemoral joint [45].

Association of knee symptoms with radiographic knee OA

In our study, frequent knee pain, presence of lack of confidence in the knee and clicking did not distinguish those with a meniscus tear alone from those with concomitant structural disease. These symptoms were not specific to those with an MRI-verified degenerative meniscal tear only. These symptoms have previously been found to be common in patients with established knee OA [14, 46, 47] supporting that these symptoms represent early signs of knee OA. Indeed, Niu et al. when developing the Meniscal Symptom Index reported that patients with concomitant knee OA had a higher prevalence of the symptoms included in the MSI compared to patients with no knee OA [20]. We showed that presence of early radiographic knee OA was associated with a higher risk of self-reported catching, swelling and stiffness later in day. No other differences in presence of symptoms were found. Swelling and stiffness are well-known symptoms in patients with knee OA. Catching however, is more commonly recognized as a mechanical symptom, usually considered emanating from a meniscus tear. A high prevalence of catching in those with knee OA indicates that the main cause of catching is not the meniscus tear in itself but instead the degenerative process of OA involving several structures of the joint. Our findings support previous reports suggesting that a degenerative meniscus tear is an early feature of knee OA [14, 48].

The selection of patients with a medial meniscus tear eligible for APM is under debate [4, 49, 50]. The presence and severity of certain knee symptoms still play a prominent role in determining eligibility for surgery. However, we found that symptoms were not able to distinguish patients with overlapping knee conditions as degenerative meniscus tears and signs of structural disease in other joint structures including bone and cartilage. In our study, catching was more likely related to OA rather than the meniscus tear itself. The unanimously use of catching as

an indication for surgery in middle-aged patients with a degenerative meniscus tear is questionable and should be reconsidered.

Conclusions

Middle-aged patients with a degenerative medial meniscus tear reported symptoms commonly associated with knee osteoarthritis. Meniscus patients reporting swelling of the knee, stiffness later in day or catching were at higher risk of having concomitant early radiographic signs of knee OA. Our findings provide support for the notion that symptoms reported by those with an MRI-verified degenerative meniscal tear are to be considered as early signs of knee OA, and that neither mechanical nor other symptoms are attributable to the degenerative meniscal tear as such, but rather to the ongoing degenerative process eventually leading to knee osteoarthritis.

References

1. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT: **Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons**. *N Engl J Med* 2008, **359**(11):1108-1115.
2. Cullen K, Hall M, Golosinskiy A: **Ambulatory surgery in the United States, 2006**. *National health statistics reports, National Center for Health Statistics* 2009, **11**:1-28.
3. Kim S: **Increase in Outpatient Knee Arthroscopy in the United States: A Comparison of National Surveys of Ambulatory Surgery, 1996 and 2006**. *J Bone Joint Surg* 2011, **93**(11):994.
4. Lyman S, Oh LS, Reinhardt KR, Mandl LA, Katz JN, Levy BA, Marx RG: **Surgical Decision Making for APM**. *Arthroscopy* 2012, **28**(4):492-201.
5. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TLN: **Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear**. *N Engl J Med* 2013, **369**(26):2515-2524.
6. Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH *et al*: **Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis**. *N Engl J Med* 2013, **368**(18):1675-1684.
7. Herrlin SV, Wange PO, Lapidus G, Hållander M, Werner S, Weidenhielm L: **Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up**. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2013, **21**(2):358-364.
8. Lim HC, Bae JH, Wang JH, Seok CW, Kim MK: **Non-operative treatment of degenerative posterior root tear of the medial meniscus**. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2009, **18**(4):535-539.
9. Herrlin S, Hållander M, Wange P, Weidenhielm L, Werner S: **Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial**. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2007, **15**(4):393-401.
10. Gauffin H, Tagesson S, Meunier A, Magnusson H, Kvist J: **Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study**. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2014, **22**(11):1808-1816.

11. McPherson K, Wennberg JE, Hovind OB, Clifford P: **Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway**. *N Engl J Med* 1982, **307**(21):1310-1314.

12. **The NHS atlas of variation in healthcare: reducing unwarranted variation to increase value and improve quality**. In. www.rightcare.nhs.uk/atlas/qipp_nhsAtlas-LOW_261110c.pdf (accessed Nov 11, 2013); 2010.

13. Fox MG: **MR Imaging of the Meniscus: Review, Current Trends, and Clinical Implications**. *Radiologic Clinics of North America* 2007, **45**(6):1033-1053.

14. Englund M, Roemer FW, Hayashi D, Crema MD, Guermazi A: **Meniscus pathology, osteoarthritis and the treatment controversy**. *Nature reviews Rheumatology* 2012, **8**(7):412-419.

15. Hegedus EJ: **Physical Examination Tests for Assessing a Torn Meniscus in the Knee: A Systematic Review With Meta-analysis**. *J Orthop Sports Phys Ther* 2007, **37**:541-550.

16. Shrier I, Boudier- Revéret M, Fahmy K: **Understanding the Different Physical Examination Tests for Suspected Meniscal Tears**. *Curr Sports Med Rep* 2010, **9**(5):284-289.

17. Konan S, Rayan F, Haddad FS: **Do physical diagnostic tests accurately detect meniscal tears?** *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2009, **17**(7):806-811.

18. Meserve BB, Cleland JA, Boucher TR: **A meta-analysis examining clinical test utilities for assessing meniscal injury**. *Clin Rehabil* 2008, **22**:143-161.

19. Ryzewicz M, Peterson B, Siparsky PN, Bartz RL: **The Diagnosis of Meniscus Tears**. *Clin Orthop Relat Res* 2007, **455**:123-133.

20. Niu NN, Losina E, Martin SD, Wright J, Solomon DH, Katz JN: **Development and preliminary validation of a meniscal symptom index**. *Arthritis Care & Research* 2011, **63**(2):208-215.

21. Yan R, Wang H, Yang Z, Ji ZH, Guo YM: **Predicted probability of meniscus tears: comparing history and physical examination with MRI**. *Swiss Medical Weekly* 2011, **141**:w13314.

22. Wagemakers HP, Heintjes EM, Boks SS, Berger MY, Verhaar JA, Koes BW, Bierma-Zeinstra SM: **Diagnostic Value of History-taking and Physical Examination for Assessing Meniscal Tears of the Knee in General Practice**. *Clin J Sport Med* 2008, **18**:24-30.

23. Abdon P, Lindstrand A, Thorngren K-G: **Statistical evaluation of the diagnostic criteria for meniscal tears**. *Int Orthop* 1990, **14**(4):341-345.

24. Roos EM: **Outcome after anterior cruciate ligament reconstruction – a comparison of patients' and surgeons' assessments**. *Scand J Med Sci Sports* 2001, **11**:287-291.

25. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM: **Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Ou**. *Arthritis Care & Research* 2011, **63**(S11):S208-S228.

26. Höher J, Bach T, Münster A, Bouillon B, Tiling T: **Does the Mode of Data Collection Change Results in a Subjective Knee Score**. *Am J Sports Med* 1997, **25**(5):642-647.

27. Lieberman JR, Dorey F, Shekelle P, Schumacher L, Thomas BJ, Kilgus DJ, Finerman GA: **Differences between patients' and physicians' evaluations of outcome after total hip arthroplasty**. *J Joint Bone Surg Am* 1996, **78**(6):835-838.

28. Stensrud S, Roos EM, Risberg MA: **A 12-Week Exercise Therapy Program in Middle-Aged Patients With Degenerative Meniscus Tears: A Case Series With 1-year Follow-up**. *J Orthop Sports Phys Ther* 2012, **42**(11):919-931.

29. Hare KB, Lohmander LS, Christensen R, Roos EM: **Arthroscopic partial meniscectomy in middle-aged patients with mild or no knee osteoarthritis: a protocol for a double-blind, randomized sham-controlled multi-centre trial**. *BMC Musculoskeletal Disorders* 2013, **14**(1):71.

30. Stensrud S, Risberg MA, Roos EM: **Knee function and knee muscle strength in middle-aged patients with degenerative meniscal tears eligible for arthroscopic partial meniscectomy**. *Br J Sports Med* 2014, **48**(9):784-788.

31. Stensrud S, Risberg MA, Roos EM: **Effect of Exercise Therapy Compared with Arthroscopic Surgery on Knee Muscle Strength and Functional Performance in Middle-Aged Patients with Degenerative Meniscus Tears: A 3-Mo Follow-up of a Randomized Controlled Trial**. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 2014.

32. Kellgren JH, Lawrence JS: **Radiological Assessment of Osteoarthrosis**. *Ann Rheum Dis* 1957, **16**(4):494-502.

33. Schiphof D, de Klerk B, Kerkhof H, Hofman A, Koes B, Boers M, Bierma-Zeinstra S: **Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis**. *Ann Rheum Dis* 2011, **70**(8):1422-1427.

34. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD: **Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure**. *J Orthop Sports Phys Ther* 1998, **28**(2):88-96.

35. Roos EM, Lohmander LS: **The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis**. *Health Qual Life Outcomes* 2003, **1**:64.

36. Roos E: **Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls**. *Osteoarthritis and Cartilage* 2001, **9**(4):316-324.

37. Charles HC, Kraus VB, Ainslie M, Hellio Le Graverand-Gastineau MP: **Optimization of the fixed-flexion knee radiograph**. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2007, **15**(11):1221-1224.

38. Kothari M, Guermazi A, Ingersleben G, Miaux Y, Sieffert M, Block J, Stevens R, Peterfy C: **Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis**. *European Radiology* 2004, **14**(9):1568-1573.

39. Schiphof D, Boers M, Bierma-Zeinstra SM: **Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis**. *Ann Rheum Dis* 2008, **67**(7):1034-1036.

40. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS *et al*: **EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis**. *Ann Rheum Dis* 2010, **69**(3):483-489.

41. Kijowski R: **Arthroscopic Validation of Radiographic Grading Scales of Osteoarthritis of the Tibiofemoral Joint**. *AJR American journal of roentgenology* 2006, **187**(3):794-799.

42. Gudbergsen H, Lohmander LS, Jones G, Christensen R, Bartels EM, Danneskiold-Samsøe B, Bliddal H, Boesen M: **Correlations between radiographic assessments and MRI features of knee osteoarthritis – a cross-sectional study**. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2012.

43. McBride GG, Constine RM, VCarson RW: **Arthroscopic partial medial meniscectomy in the older patient**. *J Bone Joint Surg* 1984, **66**:547-551.

44. Chan KK, Sit RW, Wu RW, Ngai AH: **Clinical, radiological and ultrasonographic findings related to knee pain in osteoarthritis**. *PLoS One* 2014, **9**(3):e92901.

45. Englund M, Lohmander LS: **Patellofemoral osteoarthritis coexistent with tibiofemoral osteoarthritis in a meniscectomy population**. *Ann Rheum Dis* 2005, **64**(12):1721-1726.

46. Dieppe P, Lohmander L: **Pathogenesis and management of pain in osteoarthritis**. *The Lancet* 2005, **365**(9463):965-973.

47. Bhattacharyya T, Gale D, Dewire P, Totterman S, Gale ME, McLaughlin S, Einhorn TA, Felson DT: **The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee**. *J Bone Joint Surg* 2003, **85-a**(1):4-9.

48. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T, Aliabadi P, McLennan CE, Felson DT: **Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study)**. *BMJ* 2012, **29**(345):e5339.

49. Jarvinen TL, Sihvonen R, Englund M: **Arthroscopy for degenerative knee--a difficult habit to break?** *Acta orthopaedica* 2014, **85**(3):215-217.

50. Suter LG, Fraenkel L, Losina E, Katz JN, Gomoll AH, Paltiel AD: **Medical decision making in patients with knee pain, meniscal tear, and osteoarthritis**. *Arthritis & Rheumatism* 2009, **61**(11):1531-1538.

Figures & Tables

Table 1 – Self-reported knee symptoms from KOOS commonly thought to be present in those with a meniscal tear [20, 34]

KOOS questionnaire
P1. How often do you experience knee pain?
What amount of knee pain have you experienced the last week during the following activities? - P2.Twisting/pivoting on your knee - P3. Straightening knee fully - P4. Bending knee fully - P5. Walking on flat surface - P6. Going up or down stairs - P7. At night while in bed - P8. Sitting or lying - P9. Standing upright
S1. Do you have swelling in your knee?
S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
S3. Does your knee catch or hang up when moving?
S4. Can you straighten your knee fully?
S5. Can you bend your knee fully?
S6. How severe is your knee joint stiffness after first wakening in the morning?
S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?
Q3. How much are you troubled with lack of confidence in your knee?

Table 2 – Demographics of patients with an MRI-verified meniscal tear found eligible for arthroscopic partial meniscectomy

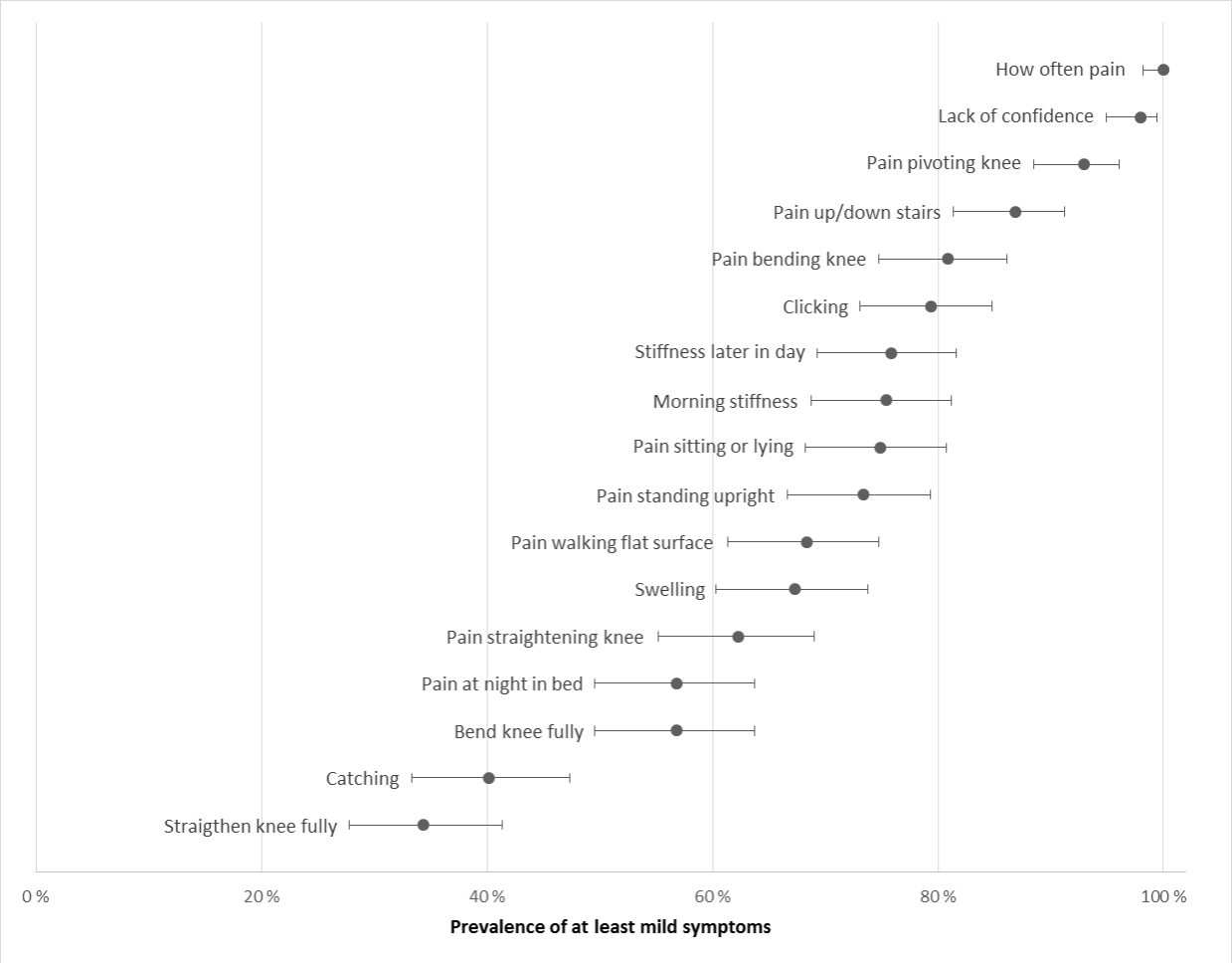
	Eligible for surgery (n=199)
Age, mean (SD)	48.4 (6.3)
Sex	
- **Male**	118 (59.3 %)
- **Female**	81 (40.7 %)
BMI, mean (SD)	26.4 (3.9)
Tibiofemoral K&L	
- **Grade 0**	128 (64.6 %)
- **Grade 1**	59 (29.8 %)
- **Grade 2**	11 (5.6 %)
KOOS, mean (SD)	
- **Pain**	61.7 (18.7)
- **Symptoms**	70.2 (17.3)
- **ADL**	72.9 (19.8)
- **Sport and recreation**	40.4 (24.7)
- **QOL**	41.7 (16.7)

Table 3 – Logistic regression analysis of association between radiographic knee OA and knee symptoms

Symptoms		Odds ratio	p	95 % CI
P1	How often pain*			
P2	Pain when pivoting/twisting	1.4	0.61	0.4 to 4.7
P3	Pain straightening knee	1.8	0.09	0.9 to 3.6
P4	Pain bending knee	1.1	0.74	0.5 to 2.5
P5	Pain walking	1.5	0.21	0.8 to 3.0
P6	Pain going up/down stairs	1.5	0.43	0.6 to 3.7
P7	Pain at night	1.5	0.21	0.8 to 2.9
P8	Pain sitting or lying	1.1	0.88	0.5 to 2.2
P9	Pain standing upright	1.4	0.41	0.7 to 2.8
S1	Swelling	2.4	0.01	1.2 to 4.9
S2	Clicking	1.6	0.27	0.7 to 3.5
S3	Catching	2.3	0.01	1.2 to 4.3
S4	Straighten knee fully	1.9	0.06	1.0 to 3.7
S5	Bend the fully	1.8	0.07	1.0 to 3.4
S6	Morning stiffness	1.4	0.34	0.7 to 2.9
S7	Stiffness later in day	2.3	0.03	1.1 to 5.0
Q3	Knee confidence	0.5	0.53	0.1 to 4.1

*Since pain was reported by all patients no analysis was carried out.

Figure 1. Prevalence of symptoms with 95% CI in patients with an MRI-verified degenerative meniscal tear and considered eligible for arthroscopic partial meniscectomy



Hare et al. BMC Musculoskeletal Disorders 2013, 14:71
http://www.biomedcentral.com/1471-2474/14/71

BMC Musculoskeletal Disorders

STUDY PROTOCOL Open Access

Arthroscopic partial meniscectomy in middle-aged patients with mild or no knee osteoarthritis: a protocol for a double-blind, randomized sham-controlled multi-centre trial

Kristoffer B Hare[1*], L Stefan Lohmander[1,2,3], Robin Christensen[1,4] and Ewa M Roos[1]

Abstract

Background: Arthroscopic partial meniscectomy has been shown to be of no benefit to patients with concomitant knee osteoarthritis, but the optimal treatment of a degenerative meniscus tear in patients with mild or no knee osteoarthritis is unknown. This article describes the rationale and methodology of a randomized sham-controlled trial to assess the benefit of arthroscopic partial meniscectomy of a medial meniscus tear in patients with mild or no knee osteoarthritis. The objective of the study is to test whether the benefit from arthroscopic partial meniscectomy in patients with knee pain, medial meniscus lesion and mild/no knee osteoarthritis, is greater after arthroscopic partial meniscectomy than following sham surgery.

Methods: We will conduct a randomized controlled trial of treatment for degenerative meniscus tears in middle-aged patients (aged 35–55 years) with an MRI-verified medial meniscus lesion and mild or no knee radiographic osteoarthritis (grade 0–2 on the Kellgren & Lawrence scale). Patients will be randomized to receive either conventional arthroscopic partial meniscectomy or a sham surgery procedure. The primary outcome will be the $KOOS_5$ derived from the '*Knee Injury and Osteoarthritis Outcome Score*' at 2 years follow-up. Secondary outcomes at 2 years will include all five individual subscales of the KOOS, a global perceived effect score, the Short-Form-36 health status score, EQ-5D for economic appraisal and objective tests of muscle strength and physical function. Radiographic knee osteoarthritis will be evaluated at 5 years.

Discussion: Demonstration of no additional benefit from arthroscopic partial meniscectomy on pain and function should lead to a change in clinical care of patients with a degenerative meniscus tear. The results of this study will provide empirical evidence for the potential benefit/harm of arthroscopic partial meniscectomy compared to a masked sham-therapeutics intervention.

Trial registration: NCT01264991

Background

A degenerative meniscus tear can be both a risk factor for knee osteoarthritis (OA) and a sign of disease [1]. The current standard treatment for a degenerative meniscus tear is arthroscopic partial meniscectomy (APM), the most commonly performed orthopedic procedure, carried out on 1 million patients annually in the USA [2]. Both meniscus injury and a meniscectomy are associated with the development of knee OA [3-5]. Previous studies have found APM to be no better than, or have no additional benefit in comparison to, sham surgery, lavage, optimized non-surgical treatment, or exercise [6-8]. In all these studies, patients with knee OA were included and the mean ages ranged from 52 to 62 - years. The benefit in a younger population from an APM procedure in a knee with a degenerative meniscus tear and mild or no knee OA is, however, uncertain and needs to be further investigated.

The benefits of the APM procedure on pain and function in patients with a degenerative meniscus tear, were

* Correspondence: kbhr@regionsjaelland.dk
[1]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
Full list of author information is available at the end of the article

firstly described in non-controlled studies from the 1980s to the 1990s [9-11] when arthroscopic procedures were gaining acceptance. However, poorly designed studies (retrospectively, use of non-validated outcome measures, small patient populations, lack of control groups and randomized allocation) have prevented firm conclusions about the effect of the APM procedure. A previous, but now withdrawn, Cochrane review from 2000 [12] concluded: *"...lack of randomized trials means that no conclusions can be drawn on the issue of surgical versus non-surgical treatment of meniscus injuries"*. At the time of this submission, there are, to our knowledge, no published high quality controlled, randomized studies that show a benefit from APM as compared to other treatment modalities (placebo, physiotherapy, medication or exercise) on pain and function in patients aged 35–55 years with a degenerative medial meniscus tear.

Both meniscus injury and meniscectomy are associated with a high risk of knee OA. Surgical resection of the meniscus leads to increased joint cartilage contact stress through altered load transmission, decreased shock absorption, and decreased joint stability [13]. Of patients who undergo either total or partial meniscectomy, 50% on average develop knee OA within 10–20 years [5]. In the elderly population in general, and in patients with radiographic knee OA but no surgery, there is a higher incidence of MRI-verified concomitant meniscus injury compared to controls [4]. It remains unclear though, whether meniscectomy increases the risk of knee OA *per se*, compared to non-surgical treatment of a meniscus injury. In this study, incidence or progression of radiographic OA will be assessed at 5 years.

Methods

Study design

The study is designed as a prospective double-blind randomized sham-controlled, multi-centre trial (RCT). Patients will be randomly allocated to receive either an APM or sham (i.e. placebo) procedure. The study is designed according to current international standards and will be reported using the recommendations in the CONSORT statement [14]. The study is approved by the Research Ethics Committee of Region Zealand, Denmark, and is consistent with the Declaration of Helsinki.

Eligible patients will be screened using standardized fixed flexion radiography of both knees, to assess the degree of radiographic knee OA. If no, or at most mild, knee OA on radiographs (Kellgren & Lawrence grades 0–2) is present, written information about the study and a 10-minute information video will be given to the patients to view at home. They will also be handed a Patient-Reported Outcomes (PRO) questionnaire to fill out at home to minimize bias. At the second contact, the patients will receive an MRI scan of the affected knee and perform tests of physical function. Thereafter, the relevant researcher and the patient will be informed of the MRI findings. If the MRI confirms a medial meniscus lesion, the patient will be invited to participate in the study. Patients not consenting to randomization will be followed as an observational cohort with consecutive PRO evaluation at the same time points as those included in the RCT. However, the observational cohort will not be part of the Intention-To-Treat (ITT) population.

At 3 months, patients will have a clinical examination, fill out PRO questionnaires, and perform objective tests of muscle strength and physical function. At 2 years, follow-up will take place under the same conditions. At 5 years, all patients will have radiography of their knees to assess possible onset or progress of knee OA from baseline. The flowchart provides a visual description of the study (Figure 1).

Purpose and hypothesis

The purpose of the present study is to determine whether the benefit from arthroscopic partial meniscectomy in patients aged 35–55 years with knee pain and an MRI-verified medial meniscus lesion, is greater after arthroscopic partial meniscectomy than following sham surgery. In addition, a 5-year follow-up of the same cohort will compare the effect of meniscectomy or sham surgery on the incidence and progression of radiographic knee OA.

We hypothesize that at 2 years, the change (improvement) in $KOOS_5$, a composite score derived from the five subscales of the KOOS, is no greater after APM than following sham surgery. Further, we hypothesize, that at 5 years the rate of radiographic knee OA incidence and progression is greater in the APM group than in the sham surgery group.

Participants

Eligibility criteria are patients between 35 and 55 years of age with knee pain for more than 2 months without significant trauma and an MRI-confirmed medial meniscus lesion. The patients must be eligible for outpatient surgery. Patients will be excluded if they are in need of acute surgery e.g. locking knees or high-energy trauma. Patients with grade 3 or 4 knee OA on the Kellgren & Lawrence classification [15,16] or knee surgery within the previous 2 years will also be excluded. Patients must be able to speak Danish and be free of any drug or alcohol abuse. Also, patients with trombophilia are excluded so as to prevent a high risk of deep venous thrombosis. The patients will be recruited through outpatient departments of the orthopedic clinics in Region Zealand on referral from general practitioners.

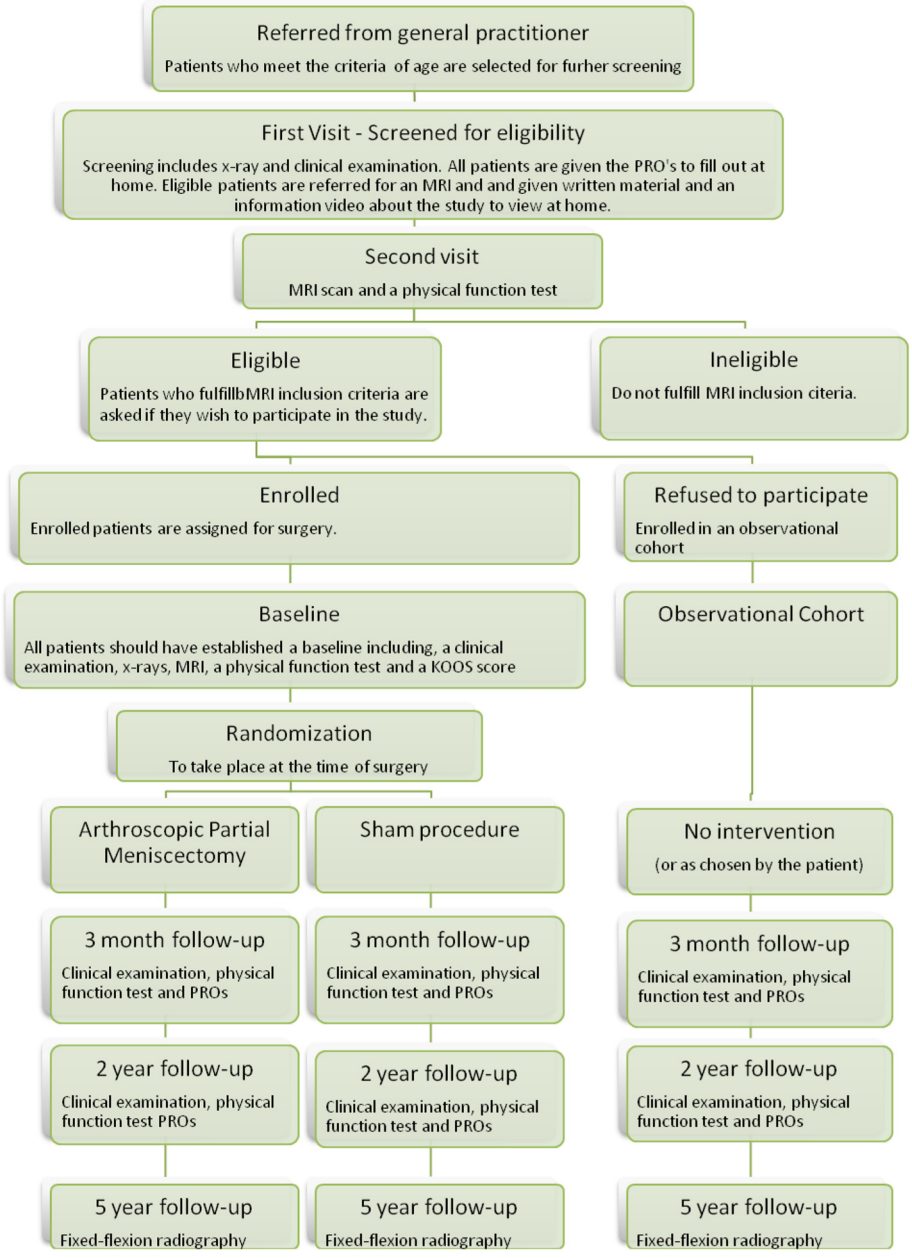


Figure 1 Study flowchart.

Interventions

Patients will be randomized to receive either arthroscopic partial meniscectomy (intervention A) or placebo procedure/sham surgery (intervention B).

Intervention A

The arthroscopic partial meniscectomy will be performed on an outpatient basis by experienced surgeons who are at least in their final year of residency or are attending orthopedic surgeons. We expect between 5–10 surgeons to be involved in the study. All arthroscopies will be performed with general anesthesia combined with local anesthesia (Bupivacain combined with Adrenalin) 20 + 20 ml extra- and intra-articularly, respectively. After general anesthesia is induced, the knee will be examined for stability. Thereafter, two standard portals on the lateral and medial sides of the ligamentum patella will be created but no outflow cannula inserted. An arthroscope will be used with a pressure-controlled irrigation system. Tourniquet use will be at the discretion of the surgeon. The strategy for the meniscectomy will be to preserve as much tissue as possible. A standard operation protocol will be used to

document possible findings in cartilage, ligaments, synovium and the medial and lateral menisci. The type, and extent of meniscus lesion will be registered and changes in the articular cartilage will be classified according to the ICRS classification [17].

Intervention B

The sham procedure will be performed under the same conditions as the arthroscopic surgery (Intervention A). In summary, the patient will be fully sedated with general anesthesia and the stability of the knee will be examined. Local anesthetic will be applied and two skin incisions will be made at the same locations and of the same size as in Intervention A. Then the knee will be manipulated as if a real arthroscopy was performed, the spillage of water and all other equipment needed for an arthroscopy will be used. A pre-recorded video of a standard arthroscopic partial meniscectomy will be played during the procedure. No instruments will enter the arthroscopy portals to avoid the possibility of deep infection, osteochondral lesions or unwanted interventions by the surgeon.

Postoperative regime (independent of concealed group allocation)

All patients in both intervention groups will be given a folder including an exercise program for postoperative patients after knee arthroscopy. The folder gives a presentation of seven different non-weight bearing exercises (for the first week after surgery) and a further three weight-bearing exercises thereafter. The exercises are for the patients to carry out at home. The patients are also recommended to start unloaded cycling, swimming or walking after 1 week, and jogging or loaded cycling after 2–3 weeks.

Primary outcome

All outcomes are listed in Table 1. The primary outcome at 2 years follow-up will be $KOOS_5$, a composite score derived from the *Knee injury and Osteoarthritis Outcome Score* (KOOS) [18,19]. The KOOS is a self-reported questionnaire comprising five subscales: pain, other symptoms, activities in daily living (ADL), function in sport and recreation and knee-related quality of life (QOL). The previous week is taken into consideration when patients are answering the questions. Standardized answer options are given (5 boxes on a Likert scale) and each question gets a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

Subsequently, $KOOS_5$ is calculated as a mean of the 5 subscale scores $[KOOS_{pain} + KOOS_{symptoms} + KOOS_{ADL} + KOOS_{sport\ \&rec} + KOOS_{QOL}]/5$.

Secondary outcomes

KOOS

All five subscales from the KOOS will be included individually as secondary outcomes to support a clinically valid interpretation of the result.

Global perceived effect

All patients are asked to answer on a seven-step global rating scale (ranging from much worse, worse, slightly worse, no difference, slightly better, better to much better) the overall improvement in their knee symptoms after the operation. This is implemented to determine the minimal important change in the PROs. A clinically important change is considered when the patient reports an improvement or worsening of at least 2 steps from 'no difference', corresponding to 'better' or 'worse' on the scale [20].

Generic patient reported outcomes

Scores on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) [21,22], which reflect the health-related quality of life (SF-36 Health Survey) – Acute version (1 week re-call period) will be used as a generic measure of patient health status at 3 and 24 - months. The SF-36 is comprised of 8 single subscale scores associated with physical and mental health.

The Euroqol 5 Dimension (EQ-5D) health score will be evaluated at baseline and at 3 and 24 months as a generic measure for economic appraisal [23,24]. EQ-5D consists of two pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems.

Performance measures

Tests of physical function will be performed at baseline and after 3 and 24 months including a one-leg jump test, maximum number of knee bends in 30 seconds and an isometric knee extension strength measurement. The patients will wear shorts, t-shirts, and sneakers. Tubigrip stockings will cover both knees to disguise scars from surgery; i.e., the test leaders will be masked regarding injured knee. In order to avoid bias from the effect of learning, randomization will be performed at each visit to determine which leg is to be tested first.

Single leg hop test

The one-leg hop will be included as a measure of physical function at a level above activities of daily living [25]. The one leg hop requires leg muscle strength, knee

Table 1 Summary of measures to be collected

Variable	Baseline T = 0 mths	Intermediate T = 3 mths	Primary endpoint T = 2 yrs	Follow-up T = 5 yrs
Baseline data				
Age – yr	@	n.a.	n.a.	n.a.
Female sex - no. (%)	@	n.a.	n.a.	n.a.
Duration of knee symptoms - months	@	n.a.	n.a.	n.a.
Height - cm	@	n.a.	n.a.	n.a.
Body weight - kg	@	n.a.	@	@
Self-efficacy scale	@	n.a.	n.a.	n.a.
Knee injury and Osteoarthritis Outcome Score (KOOS)				
Pain – range: 0-100	@	@	@	@
Symptoms - range: 0-100	@	@	@	@
Function in daily living – range: 0-100	@	@	@	@
Function in sport and recreation – range: 0-100	@	@	@	@
Knee related Quality of life – range: 0-100	@	@	@	@
EQ-5D				
Global disease descriptive system	@	@	@	@
VAS patient global assessment of disease status - 0-100	@	@	@	@
Short-Form-36 health survey - acute form				
Physical component summary – range: 0-100	@	@	@	@
Mental component summary – range: 0-100	@	@	@	@
Global Perceived Effect				
7 step scale ranging from much worse to much better	n.a.	@	@	@
Standardized knee radiographic with SynaFlexer				
JSW and presence of osteophytes	@	n.a	n.a	@
Performance measures				
Single leg hop test	@	@	@	n.a.
Knee-bending test	@	@	@	n.a.
Isometric knee extensor strength	@	@	@	n.a.

@ = Assessed; n.a. = not assessed; VAS = Visual Analogue Scale; JSW = joint space width.

stability and confidence in knee function [26]. Subjects will perform two practice trials and then three test trials on each leg with hands behind their back. The best of the three test trials will be used. An additional trial will be performed if the patients improve more than 10 centimeters from trial two to trial three [27].

Knee-bend test

The maximum number of knee-bends performed in 30 - seconds will be included as a measure of one-legged physical function required in daily life. This test requires fast changes between concentric and eccentric work and resembles stepping down a stair and is valid and reliable in meniscectomized patients [27].

Isometric knee extensor strength

Maximum knee-extension force will be measured using a hand-held dynamometer (Powertrack Commander). Patients will sit at the end of the examination couch with hip angle at 90° and knee angle at 60°. A large Velcro strap will be attached to the examination couch and the patient's ankle will be perpendicular to the lower leg. The transducer will be placed at the front of the ankle under the Velcro strap to measure knee extension force. Patients will be instructed to contract "as forcefully as possible" with a gradual increase in force and strong verbal encouragement will be provided during the contractions. They will perform 3 contractions separated by a 60-second pause, and the highest value will be used as the result.

The reliability of the isometric muscle tests with a hand-held dynamometer has been reported to be satisfactory [28-30]. The knee extension strength will be expressed as maximal voluntary torque per kilo of body mass using the external lever-arm length and body mass of each patient.

Radiographic OA

To evaluate progression of knee OA, a fixed-flexion radiography procedure, with use of SynaFlexer [31], will be performed at baseline and after 5 years. This provides radiography at the exact same position and has been validated in determining joint space width (JSW) in knee osteoarthritis [32]. A single reader will score all the study films from baseline and 5-year follow-up and will be blinded to all clinical and questionnaire data and the baseline x-ray result but not to the sequence of the x-rays. A score will be assigned to each x-ray based on JSW and presence of osteophytes using a standard atlas [33].

Exploratory outcomes

A questionnaire of patient self-efficacy modified from the Danish Arthritis Self-Efficacy Scale to suit this somewhat younger age group (not formally validated) and a question on patient expectations will be included. Demographic data will also be collected. Furthermore, participating patients will be asked two questions regarding their study participation. 1) "Which reason is the most motivating for your participation?" and 2) "Which information was the most useful when deciding?" Physical therapy prescribed by either a general practitioner or a research staff member will be carefully monitored with regard to the number of exercise sessions.

Adverse events

Adverse events (not necessarily implying causality) will be registered in both treatment arms. A priori defined adverse events are: superficial infection, nerve or vessel injury, deep infection, compartment syndrome, deep venous thrombosis, myocardial infarction, stroke, and death. Re-arthroscopy is also considered an adverse event. Adverse events will be gathered from patients themselves, from the patient record review, and from the Danish National Patient Index (NPI) at the 3 and 24 - months follow-ups.

Sample size

The sample-size calculation is based on the assumed superiority of the arthroscopic procedures over the sham procedure. For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05, assuming a common standard deviation (SD) of 15 in the $KOOS_5$ score, a sample size estimation of the ITT population indicated that 36 individuals per group would be required to obtain a power of at least 80% to detect a minimal important change (MIC) of 10 $KOOS_5$ score units. The MIC of 10 points and SD of 15 is based on findings from similar patient groups and interventions [19].

Following these estimations, it was decided to include 80 individuals in total (40 patients in each group), allowing for a 10% drop-out rate.

Randomization

We will generate the two comparison groups using simple randomization, with an equal allocation ratio (1:1), by referring to a computer-generated table of random numbers. To ensure an equal distribution in the two groups, we will use a block randomization, using blocks of 4 and 6. Participants will be stratified for treatment centre. To ensure concealment of the assigned intervention, the surgeon will obtain a sealed envelope containing the participant's assigned intervention after the patient is in the operating suite and has been fully sedated. The consecutively numbered envelope will be retrieved from a briefcase located at the actual operating theatre. The above mentioned allocation sequence will be generated by an external co-investigator, the enrolment will be performed by the first author and the assignment will be at the operating room where the envelope will be opened by the surgeon.

Blinding

The RCT will be a double-blind trial. All study personnel and participants will be blinded to the intervention, except for the surgeons and other operating theatre personnel, who do not have any other role in the study.

Statistical methods

Treatment groups will be examined for comparability at baseline with respect to demographic and prognostic factors. An ITT analysis based on all the randomized individuals - for the efficacy measures - will apply. Comparisons between groups of the primary end point will include all repeated measures and be analyzed with the use of a mixed effects model, with random factors for participant and centre.

Clinically important or relevant difference for the $KOOS_5$ and KOOS subscales were chosen as 10/100 points. Thus a confidence interval excluding differences greater than 10 units between groups will be interpreted as indicating the absence of a clinically meaningful difference. This means that, if the 95% Confidence Interval around the group mean difference does not include a *potential* clinical benefit of 10 KOOS points, then we will then consider the therapeutic strategies equal.

Patients in the sham group who, later during the course of the study, may have an APM procedure will, according to the ITT principle, still be analyzed in the group to which they were originally allocated. Secondarily, all analyses will be supported/interpreted in the context of the corresponding results according to the per protocol populations.

Treatment failure

No a priori criteria for cross-over are given. Should a patient contact the department because of unbearable

symptoms they will be un-blinded and in case of having had placebo surgery they will be offered a new arthroscopy. These patients will be treated as cross-overs and still be included in the study. In case of the patient having had arthroscopic surgery in the first place the patient will be referred to the responsible surgeon who will be in charge of referring to further surgical or non-surgical treatment and/or investigation. Both patient groups will be asked to fill out a KOOS questionnaire at the extra visit and will continue to be followed at the follow-ups determined by the study protocol."

Discussion

Degenerative meniscus tears are common and related to the development of knee osteoarthritis [1,3-5]. Arthroscopic partial meniscectomy is the current treatment of choice in patients with mild or no concomitant knee osteoarthritis but this has not been formally evaluated in randomized placebo controlled trials.

The outcome of this study will show whether arthroscopic partial meniscectomy is a viable treatment modality. Inclusion of a sham surgery treatment will enable us to study the effect of the partial meniscectomy per se. The findings of this research will potentially be of international importance and will be readily translatable into clinical practice, irrespective of the results. If our results are in favor of APM, we will have evidence to support continued use of APM in this patient category. If, on the other hand, our results indicate that the efficacy of APM is less than placebo (and it may do more harm), then this would also significantly impact upon current practice and APM should not be the treatment of choice in middle-aged patients with an MRI-verified meniscus tear and mild or no knee osteoarthritis. No difference between APM and placebo might not be regarded as a strong enough piece of evidence to stop operating on middle-aged patients with meniscus tear and mild OA. However, a finding of superiority for arthroscopy would certainly increase the tendency to treat these patients surgically, and a finding of superiority for placebo would discourage operative treatment. Finding no effect of APM would support the notion that a degenerative meniscus tear is the first sign of future knee OA. If so, the treatment of choice should conform to treatment guidelines for mild and moderate knee OA.

The study design has some limitations. The surgeon's level of experience may differ since we need to allow general orthopedic surgeons to operate and not only sports surgeons. However, this has the benefit of an increased external validity. The population in the study is somewhat heterogeneous, from patients with no osteoarthritis to patients with mild osteoarthritis. We do not know whether a meniscus tear has different etiology in those with and without radiographic OA and how this may affect the result. There is no consensus on what defines a symptomatic meniscus tear or whether or not to perform an MRI before surgery. Clinical tests (McMurray, Apley, etc.) have not been proven to diagnose a meniscus tear accurately [34]. Therefore in this study, we included patients with knee pain and an MRI-confirmed medial meniscus lesion but there is a risk that, in some patients, symptoms may actually not be caused by the meniscus tear. Further, other patients who would otherwise have undergone a knee arthroscopy may be excluded due to the MRI not confirming a suspected meniscus tear. Another limitation of using MRI as a diagnostic tool is the risk of a false positive result. If the patient will be randomized to a sham operation, this error will never be discovered. We chose not to perform a diagnostic arthroscopy in the sham group primarily to reduce the risk of deep infection which we find would be unacceptable for a sham intervention. Other reasons were to avoid any accidental osteochondral lesions from the arthroscope and unwanted intervention from the surgeons.

The study does not include an activity score. A literature search revealed a lack of valid self-reported instruments of activity level for this diverse middle-aged population of varying physical activity levels. Since providing patients with accelerometers was not an option due to logistic reasons, we have not included any measure of activity level in this trial.

In spite of the above limitations, this study has strong methodological rigor through its design as a double-blinded placebo controlled RCT, compared to the earlier non-controlled studies of degenerative medial meniscus tears.

Ethical considerations are important when performing a surgical placebo controlled study. One may ask, 'Is it ethical to perform placebo-controlled RCTs of surgery?' since the initial precept in medicine is "First, do no harm". An equally valid question though, may be, 'Is it ethical not to perform placebo-controlled RCTs within orthopedics [35] and instead, potentially perform under-researched operations which may not benefit the patient, or worse, do harm?'

A recent study of vertebroplasty [36,37] has effectively shown how a placebo-controlled surgical trial can evaluate a given procedure that has been adopted widely despite an absence of robust evidence. Currently, there are three reasons to perform yet another placebo-controlled arthroscopy study, in addition to the one performed by Moseley and collaborators (2003). Firstly, the current study will focus on younger patients; secondly, these patients are at an earlier stage of disease and have not yet developed severe knee OA; and thirdly, a replication study is required to make Moseley's evidence more convincing.

Abbreviations
OA: Osteoarthritis; APM: Arthroscopic partial meniscectomy; RCT: Randomized controlled trial; KOOS: Knee injury and osteoarthritis outcome score; PRO: Patient-reported outcome; QOL: Quality of life.

Competing interests
The authors declare that they have no competing interests.

Authors' contribution
KH, SL and ER participated in the conception and design of the study. KH will participate in the recruitment of participants. KH, SL, RC and ER were involved in drafting the manuscript or revising it, all authors read, commented, and approved the manuscript.

Authors' information
KH: MD, PhD student, Research Unit for Musculoskeletal Function and Physiotherapy at the Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; SL: MD, PhD, Professor at the Department of Orthopedics, Lund University, Sweden, Research Unit for Musculoskeletal Function and Physiotherapy at the Institute of Sports Science and Clinical Biomechanics and Department of Orthopedics and Traumatology, University of Southern Denmark, Odense, Denmark; RC, MSc, PhD, Associate Professor of Statistics in Medicine, Musculoskeletal Statistics Unit, the Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Frederiksberg, Copenhagen F, Denmark; ER: PT, PhD, Professor and Head of Research Unit for Musculoskeletal Function and Physiotherapy at the Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark.

Acknowledgements
The authors would like to acknowledge the support of the University of Southern Denmark, Odense; the Orthopedic Departments of Slagelse and Næstved Hospital; The Research unit of Hospital South, Region Zealand; Edith and Henrik Henriksens Memorial Fund for a grant (December 2010), Region Zealand Health Scientific Research Fund for a grant (November 2010); Research Fund of Hospital South for funding of KH; and the Musculoskeletal Statistics Unit at the The Parker Institute is supported by unrestricted grants from the Oak Foundation.

Author details
[1]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark. [2]Department of Orthopedics, Clinical Sciences Lund, University of Lund, Lund, Sweden. [3]Department of Orthopedics and Traumatology, University of Southern Denmark, Odense, Denmark. [4]Musculoskeletal Statistics Unit, the Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Frederiksberg, Copenhagen, Denmark.

Received: 28 February 2012 Accepted: 20 February 2013
Published: 25 February 2013

References
1. Englund M, Roos EM, Lohmander LS: **Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls.** *Arthritis Rheum* 2003, **48**(8):2178–2187.
2. Cullen K, Hall M, Golosinskiy A: **Ambulatory surgery in the United States, 2006.** *National health statistics reports, National Center for Health Statistics* 2009, **11**.
3. Englund M: **The Role of the Meniscus in Osteoarthritis Genesis.** *Rheumatic Disease Clinics of North America* 2008, **34**(3):573–579.
4. Englund M, Guermazi A, Roemer FW, Aliabadi P, Yang M, Lewis CE, Torner J, Nevitt MC, Sack B, Felson DT: **Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The multicenter osteoarthritis study.** *Arthritis Rheum* 2009, **60**(3):831–839.
5. Englund M, Lohmander LS: **Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy.** *Arthritis Rheum* 2004, **50**(9):2811–2819.
6. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP: **A controlled trial of arthroscopic surgery for osteoarthritis of the knee.** *N Engl J Med* 2002, **347**(2):81–88.
7. Kirkley A, Birmingham TB, Litchfield RB, Giffin R, Willits KR, Wong CJ, Feagan BG, Donner A, Griffin SH, D'Ascanio LM, *et al*: **A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee.** *N Engl J Med* 2008, **359**(11):1097–1107.
8. Herrlin S, Hållander M, Wange P, Weidenhielm L, Werner S: **Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial.** *Knee Surg Sports Traumatol Arthrosc* 2007, **15**(4):393–401.
9. Jackson RW, Rouse DW: **The Result of Partial Arthroscopic Meniscectomty in Patients Over 40 Years of Age.** *J Bone Joint Surg Br* 1982, **64-B**(4):481–485.
10. Bonamo JJ, Kessler KJ, Noah J: **Arthroscopic meniscectomy in patients over the age of 40.** *Am J Sports Med* 1992, **20**(4):422–429.
11. McBride GG, Constine RM, VCarson RW: **Arthroscopic partial medial meniscectomy in the older patient.** *J Bone Joint Surg Br* 1984, **66:**547–551.
12. Howell J, Handoll H: **Surgical treatment for meniscal injuries of the knee in adults.** *Cochrane Database Syst Rev* 1999, **1:**1–24.
13. Seedhom B, Hargreaves D: **Transmission of the load in the knee joint with special reference to the role of the meniscus. Part I-II.** *Eng Med* 1979, **4:**207–228.
14. Schulz KF, Altman DG, Moher D: **CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.** *BMJ* 2010, **340**(mar23 1):c332–c332.
15. Kellgren JH, Lawrence JS: **Radiological Assessment of Osteoarthrosis.** *Ann Rheum Dis* 1957, **16**(4):494–502.
16. Schiphof D, de Klerk B, Kerkhof H, Hofman A, Koes B, Boers M, Bierma-Zeinstra S: **Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis.** *Ann Rheum Dis* 2011, **70**(8):1422–1427.
17. *Clinical Cartilage Injury Evaluation System.* http://www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf.
18. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD: **Knee Injury and Osteoarthritis Outcome Score (KOOS)–development of a self-administered outcome measure.** *J Orthop Sports Phys Ther* 1998, **28**(2):88–96.
19. Roos EM, Lohmander LS: **The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis.** *Health Qual Life Outcomes* 2003, **1:**64.
20. Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V, Brooks P, Tugwell P: **Minimal Clinically Important Differences: Review of Methods.** *J Rheumatol* 2001, **28**(2):406–412.
21. Ware JE, Sherbourne CD: **The MOS 36-item Short-Form Health Survey (SF-36): I. Conceptual Frame and Item Selection.** *Medical Care* 1992, **30**(6):473–483.
22. McHorney CA, Ware JE, Raczek AE: **The MOS 35-item Short Form Health Survery (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs.** *Medical Care* 1993, **31**(3):247–263.
23. Group TE: **Euroqol - a new facility for the measurement of health-related quality of life.** *Health Policy* 1990, **16:**199–208.
24. Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM: **Generation of a Danish TTO value set for EQ-5D health states.** *Scand J Public Health* 2009, **37**(5):459–466.
25. Noyes FRBS, Mangine RE: **Abnormal lower limb symmetry determined by function hop tests after anterior cruciate ligament rupture.** *Am J Sports Med* 1991, **19:**513–518.
26. Tegner Y, Lysholm J, Lysholm M, Gillquist J: **A performance test to monitor rehabilitation and evaluate anterior cruciate ligament injuries.** *Am J Sports Med* 1986, **14:**156–159.
27. Bremander AB, Dahl LL, Roos EM: **Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis.** *Scand J Med Sci Sports* 2006, **17:**120–127.
28. Thorborg K, Petersen J, Magnusson SP, Hölmich P: **Clinical assessment of hip strenght using a hand-held dynamometer is reliable.** *Scand J Med Sci Sports* 2009, **20:**493–501.
29. Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T: **Loss of Knee-Extension Strength Is Related to Knee Swelling After Total Knee Arthroplasty.** *Arch Phys Med Rehabil* 2010, **91**(11):1770–1776.

30. Roy M-AG, Doherty TJ: **Reliability of Hand-Held Dynamometry in Assessment of Knee Extensor Strength After Hip Fracture.** *Am J Phys Med Rehabil* 2004, **83**(11):813–818.
31. Charles HC, Kraus VB, Ainslie M: **Hellio Le Graverand-Gastineau MP: Optimization of the fixed-flexion knee radiograph.** *Osteoarthr Cartil* 2007, **15**(11):1221–1224.
32. Kothari M, Guermazi A, Ingersleben G, Miaux Y, Sieffert M, Block J, Stevens R, Peterfy C: **Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis.** *Eur Radiol* 2004, **14**(32):1568–1573.
33. Altman R, Gold G: **Atlas of individual radiographic features in osteoarthritis, revised1.** *Osteoarthr Cartil* 2007, **15:**A1–A56.
34. Hegedus EJ: **Physical Examination Tests for Assessing a Torn Meniscus in the Knee: A Systematic Review With Meta-analysis.** *J Orthop Sports Phys Ther* 2007, **37:**541–550.
35. Flum DR: **Interpreting Surgical Trials With Subjective Outcomes.** *J Am Med Assoc* 2006, **296**(20):2483–2485.
36. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt CJ, Graves SE, Staples MP, Murphy B: **A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures.** *N Engl J Med* 2009, **361**(6):557–568.
37. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, *et al*: **A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures.** *N Engl J Med* 2009, **361**(6):569–579.

doi:10.1186/1471-2474-14-71
Cite this article as: Hare *et al.*: Arthroscopic partial meniscectomy in middle-aged patients with mild or no knee osteoarthritis: a protocol for a double-blind, randomized sham-controlled multi-centre trial. *BMC Musculoskeletal Disorders* 2013 **14**:71.

Hare et al. Trials 2014, 15:167
http://www.trialsjournal.com/content/15/1/167

TRIALS

RESEARCH Open Access

The challenge of recruiting patients into a placebo-controlled surgical trial

Kristoffer B Hare[1,2*], L Stefan Lohmander[1,3] and Ewa M Roos[1]

Abstract

Background: Randomized placebo-controlled trials represent the gold standard in evaluating healthcare interventions but are rarely performed within orthopedics. Ethical concerns or well-known challenges in recruiting patients for surgical trials in general have been expressed and adding a placebo component only adds to this complexity. The purpose of this study was to report the challenges of recruiting patients into an orthopedic placebo-controlled surgical trial, to determine the number of patients needed to be screened and allocated in order to include one participant into the trial, and to identify reasons associated with participation in a placebo-controlled randomized surgical trial.

Methods: Data were extracted from an ongoing placebo-controlled randomized controlled trial (RCT) on meniscectomy versus placebo surgery. We calculated the number of patients needed to be screened in order to include the required number of participants into the RCT. Participating patients were asked about their rationale for joining the study and which type of information was most useful for deciding upon participation.

Results: A total of 476 patients entered the screening group, of which 190 patients fulfilled the inclusion and exclusion criteria. 102 patients declined to participate in the study due to various reasons and 46 were later excluded (no meniscus lesion on the magnetic resonance imaging scan or withdrawn consent). A total of 40 patients were finally included in the RCT. To include one patient into the RCT, 11.9 individuals needed to be screened. A total of 69% of participating patients considered the oral information to be the most important and the most common reason for participating was the contribution to research (90%).

Conclusions: Patients are willing to participate in an orthopedic placebo-controlled surgical trial. Oral information given by the surgeon to the patient and the contribution to research are important aspects to enhance patient recruitment.

Trial registration: ClinicalTrials.gov NCT01264991, registered 21 December 2010.

Keywords: Feasibility, Placebo, Surgery, Recruitment, Trial

Background

Randomized controlled trials (RCTs) represent the gold standard in evaluating healthcare interventions. The randomization of treatment and blinding of group allocation to the investigator and participants, possibly by use of a placebo, reduces bias [1]. Though this design is considered gold standard in therapeutic trials this has not been the case within the field of surgery. Ethical concerns [2,3] or well-known challenges in recruiting patients for surgical trial in general [4,5] have been expressed and adding a placebo component only adds to this complexity.

We are not aware of any studies on the challenge of recruiting patients for a placebo-controlled orthopedic trial, specific screening procedures for identifying eligible patients, or motivation of patients to participate in a placebo-controlled orthopedic trial. One study on feasibility and acceptance showed that an orthopedic placebo-controlled trial could be conducted in principle, albeit with difficulty [6]. The challenge of recruitment for an orthopedic RCT comparing rehabilitation plus early surgery with rehabilitation plus optional later surgery for an

* Correspondence: kbhr@regionsjaelland.dk
[1]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark
[2]Department of Orthopedics, Slagelse Hospital, Ingemannsvej 18, 4200 Slagelse, Region Zealand, Denmark
Full list of author information is available at the end of the article

acute ACL (anterior cruciate ligament) tear have been reported, [7] but similar reports from placebo-controlled trials are lacking. Earlier placebo-controlled orthopedic studies have reported a recruitment rate between 35 and 71% [8-10] but no information exists on patient's preferences and determinants of willingness to participate in an orthopedic placebo-controlled study.

Arthroscopic partial meniscectomy (APM) is the most commonly performed orthopedic procedure, carried out on 1 million patients annually in the United States [11]. The mean age in most studies is around 50 years of age [8,12-14], indicating the vast majority of procedures being performed in patients with a degenerative disease. Both meniscus injury and meniscectomy are associated with the development of knee osteoarthritis (OA) [15-17]. Previous studies in patients with or without concomitant OA have found APM to be no better than, or have no additional benefit in comparison to, placebo surgery, lavage, optimized non-surgical treatment, or exercise [8,12-14].

This report describes the challenges of recruiting patients into an ongoing multicenter RCT [18] comparing APM to a placebo surgery of degenerative meniscus tears in a younger age group (between 35 and 55 years of age) at an earlier stage of disease. We provide the number of patients needed to be screened (NNS), and the number of patients needed to be allocated (NNA), in order to include the required number of participants into the RCT. We further identify the reasons associated with participation in a placebo-controlled randomized surgical trial by asking why patients were willing to participate and which type of information was most useful for deciding upon participation.

Methods

We recruited and screened patients aged between 35 and 55 years, having a magnetic resonance imaging (MRI) confirmed medial meniscus lesion and at least two months of knee pain without any previous significant trauma. Eligible patients were randomized to placebo surgery or APM after having agreed to participate in the RCT and after providing signed informed consent (Table 1).

Both APM and the placebo surgery were performed under general anesthesia but only skin incisions equivalent to two standard portals were performed in the placebo group.

The complete design and methodology of the study have been published [18]. The study is approved by the Research Ethics Committee of Region Zealand, Denmark, and is consistent with the Declaration of Helsinki.

Screening strategies

Patients referred from general practitioners were screened for eligibility by the principal investigator, an orthopedic surgeon in residency. If eligible, oral and written information were given about the study including a 12-minute DVD to view at home. A few days later the patients were contacted by telephone and provided temporary consent by phone, and if willing to participate they were referred for an MRI to confirm a meniscus lesion. If their MRI confirmed a medial meniscus lesion the patient provided written consent, was included in the study, and signed up for surgery if still willing to participate. The strategy of asking patients to participate before performing an MRI was chosen since an MRI is not routinely performed before an arthroscopy in Denmark.

Table 1 Inclusion and exclusion criteria in the RCT of APM versus placebo surgery of degenerative meniscus tears

Inclusion criteria	
1.	Knee pain > 2 months without significant trauma
2.	MRI confirmed medial meniscus lesion
3.	Age 35-55
4.	Eligible for outpatient surgery
Exclusion criteria	
1.	Need for acute surgery, i.e. locking knees, high energy trauma
2.	Symptoms from other musculoskeletal disorder overriding symptoms of the knee
3.	Grade 3 or 4 knee OA on the Kellgren-
4.	Lawrence classification
5.	Knee surgery within the last 2 years
6.	BMI > 35
7.	Ischemic heart disease
8.	Diabetic late complications
9.	Thrombophilia
10.	Pregnancy
11.	Unable to speak Danish
12	Drug or alcohol abuse

APM, arthroscopic partial meniscectomy; BMI, Body Mass Index; OA, osteoarthritis; RCT, randomized controlled trial.

Patient information

Patients eligible for an MRI all received the same oral and written information. The oral information was given by the principal investigator in a standardized way. Patients were informed of the nature of a degenerative meniscus lesion, the treatment options, and hereunder surgery. They were informed about the lack of evidence for the effects of meniscus surgery in older age groups. They were then informed of the lack of trials in their age group, the need for a study, the general concept of the placebo effect, and the design of the current study, including information that placebo surgery would mean that no intervention on their meniscus tear would be performed.

The written information was identical to the oral information apart from formal information about study origin, study investigators, information on possible adverse events (most common infection and deep venous thrombosis) and other treatment modalities (such as exercise).

A 12-minute DVD was given to all eligible patients prior to the MRI to further ensure uniform dissemination of information to all patients. The video described the background for the study, the amount of involvement for participating and showed interviews of three different orthopedic surgeons with extensive experience within knee surgery giving their view on the condition and arthroscopic meniscus surgery.

Statistics

The number needed to screen (NNS) and the number needed to allocate (NNA) are concepts used and described in previous studies [7,19,20]. The NNS was calculated by dividing the number of patients screened for eligibility with the number of patients included in the trial. Similarly the NNA was calculated by dividing the number of allocated patients with the number of included patients. All patients eligible for inclusion were regarded as allocated. The NNS and NNA provided an estimate of how many patients were needed to be screened and allocated to include one patient into the trial. Multiplied with the *a priori* determined sample size, the NNS gives an estimate of how many patients needed to be screened and the NNA an approximation of the total number of eligible patients necessary.

All participating patients were asked about their rationale for joining the study: wanting to contribute to research, wanting an operation no matter which type, or other, with room for elaboration. They were also asked which kind of information had been most beneficial in deciding whether or not to participate: the oral information given by the orthopedic surgeon, the written information, or the 12-minute DVD. The proportions of these answers were calculated and reported with 95% confidence intervals (95% CI).

Results

Since the start of the study, 476 patients with a suspicion of medial meniscus injury referred from their general practitioner entered the screening group. A total of 190 patients fulfilled the inclusion and exclusion criteria and were thus eligible for an MRI. However, of these, 102 patients declined to participate in the study. More specifically, 77 did not wish to participate after reviewing the patient information, the reasons being: a) not wanting placebo surgery (38%), b) the risk of undergoing a secondary operation if allocated to the placebo group (21%), and c) not wanting surgery at all (19%). A small number (5%) did not want to participate in any scientific study and 17% had other reasons, mostly work-related. A total of 25 patients declined participation before reviewing

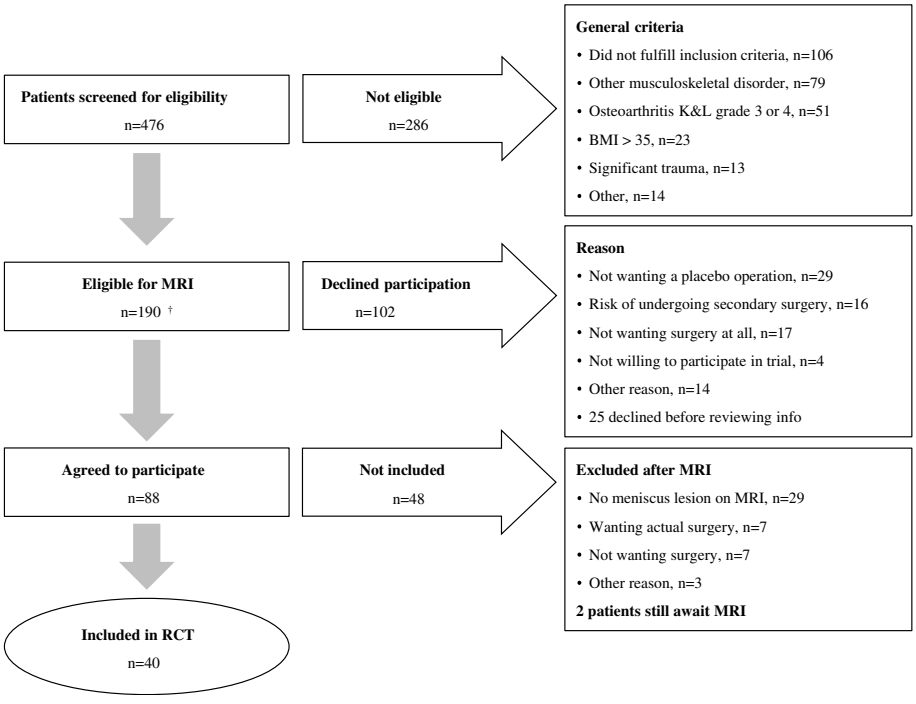


Figure 1 Flowchart of the recruitment process in this RCT. †4 patients underwent an MRI which was negative before being informed of the study. BMI, Body Mass Index; RCT, randomized controlled trial.

the patient information and their reasons for declining participation were not collected. In addition, 46 were excluded after no visible meniscus tear was seen on MRI. Finally, 40 patients were included in the RCT (Figure 1). To include one patient into the RCT, 11.9 individuals with a suspected meniscus lesion needed to be screened. Similarly, the NNA was 4.8 individuals eligible for inclusion (prior to MRI) needed in order to include one patient in the RCT.

Of the 40 included patients, the most common reason for participating was the contribution to research (90% (80 to 100, 95% CI)) compared to other reasons (10% (0 to 20, 95% CI), $P < 0.001$). A total of 69% (54 to 84, 95% CI) of participating patients considered the oral information from the orthopedic surgeon as the most important compared to the written information and DVD (31% (16 to 46, 95% CI), $P < 0.05$).

Discussion

There is a great need for randomized controlled, including placebo-controlled, orthopedic trials. The most common reasons for this lack of placebo-controlled surgical RCTs include ethical issues and difficulty in recruiting patients. The recruitment of patients into orthopedic RCTs is a well-recognized challenge [4,5] and adding a placebo component to the trial potentially further complicates recruitment.

In our placebo-controlled study we showed that 46% of patients fulfilling clinical eligibility criteria were willing to participate in a placebo-controlled arthroscopy trial, fully aware they would have general anesthesia and possibly surgery without any real intervention being performed. These patients weighted the oral information given as more important than the written information and the 12-minute DVD when deciding whether to participate or not. They also reported that the contribution to science was the main reason for participating, which is similar to other studies [21-23].

A NNS of 11.9 is high, compared to other trials of orthopedic surgery. Buchbinder *et al.* [9] reported a NNS of 6 for their placebo-controlled RCT of vertebroplasty and Frobell *et al.* [7] reported an NNS of only 5.5 in their RCT study comparing rehabilitation plus early surgery with rehabilitation plus optional later surgery for an acute ACL injury. One other study by Katz *et al.* [12] comparing APM in combination with physiotherapy or physiotherapy alone reported a NNS of 41.1, indicating only a minority of patients meeting the inclusion criteria. The NNS is markedly affected by the screening strategy, pathoanatomy and clinical inclusion criteria, and planned interventions, and hence will vary between different trials for different conditions. In this study the high NNS was influenced by the fact that the screening was made on a broad population of patients referred from general practitioners less experienced in knee examination and before any imaging was performed. Thus patients with symptoms and clinical signs not related to an MRI-verified meniscus injury constituted a large part of the screening population. Performing an MRI after clinical screening meant that more patients had to be screened. Future clinical trials of meniscus surgery may consider performing an MRI earlier during the screening process to lower the number of patients seen by the clinician. Degenerative meniscus tears are difficult to detect and assess by clinical examination alone [24] and in the present study an MRI failed to show a meniscus tear in 33% of eligible symptomatic patients willing to participate, confirming a poor correlation between clinical signs and MRI findings in this patient group [16,25].

The NNA of 4.8 was also higher than other comparable studies: the NNA for the vertebroplasty trial [9] was 2.1, for the ACL treatment trial [26] 1.6, and for another placebo-controlled study of medial degenerative tears by Sihvonen *et al.* [10] the NNA was only 1.4. Despite this, it still took five years in five different centers to include 146 patients. That is approximately six patients included per year per center. This could suggest that definition of eligibility and/or timing of consent were different than from our study. The NNA in the study by Katz *et al.* [12] was 3.8, mainly because approximately 60% of the patients declined to participate. In our study also more than half the patients declined to participate. This is no different from other placebo-controlled trials on already established surgical procedures and emphasizes the importance of evaluating the effect from surgical interventions in a similar fashion as for other therapeutic trials [27], alas prior to introducing a new surgical procedure. Another reason for the high NNA was that 17 patients withdrew their initial consent after their MRI. Half of these patients withdrew consent because, although having a positive MRI finding, their symptoms had regressed and they no longer experienced a need for surgery, and the other half because they would not risk receiving a placebo operation.

Conclusions

In conclusion we have shown that patients are willing to participate in an orthopedic placebo-controlled surgical trial. Challenges remain to improve screening procedures for an improved feasibility, and pilot studies are critical for a realistic assessment of NNS and NNA. We recommend that when recruiting patients for a placebo-controlled surgical trial, focus should be on the oral information given by an orthopedic surgeon and the patient's contribution to science should be emphasized.

Abbreviations

ACL: Anterior cruciate ligament; APM: Arthroscopic partial meniscectomy; CI: Confidence interval; DVD: Digital video disc; MRI: Magnetic resonance imaging; NNA: Number needed to allocate; NNS: Number needed to screen; OA: Osteoarthritis; RCT: Randomized controlled trial.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
KBH participated in the design of the study, was responsible for data collection and drafted the manuscript. LSL participated in the design of the study and helped to draft the manuscript. EMR participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements
The authors would like to acknowledge the support from the University of Southern Denmark, Odense; the Orthopedic Departments of Slagelse and Næstved Hospital; the Research Unit of Hospital South, Region Zealand; Edith and Henrik Henriksens Memorial Fund for a grant (December 2010); Region Zealand Health Scientific Research Fund for a grant (November 2010); and Research Fund of Hospital South for funding of KBH.

Author details
[1]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark. [2]Department of Orthopedics, Slagelse Hospital, Ingemannsvej 18, 4200 Slagelse, Region Zealand, Denmark. [3]Department of Orthopedics, Clinical Sciences Lund, University of Lund, Paradisgatan 2, 221 00 Lund, Sweden.

Received: 14 December 2013 Accepted: 30 April 2014
Published: 13 May 2014

References
1. Armitage P: **The role of randomization in clinical trials.** *Stat Med* 1982, **1**:345–352.
2. London AJ, Kadane JB: **Placebo that harms: sham surgery controls in clinical trials.** *Stat Methods Med Res* 2002, **11**:413–427.
3. Macklin R: **The ethical problems of sham surgery in clinical trials.** *N Engl J Med* 1999, **341**:992–996.
4. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien P-A, Reeves BC, Seiler CM: **Challenges in evaluating surgical innovation.** *Lancet* 2009, **374**:1097–1104.
5. McLeod RS: **Issues in surgical randomized controlled trials.** *World J Surg* 1999, **23**:1210–1214.
6. Campbell MK, Entwistle VA, Cuthbertson BH, Skea ZC, Sutherland AG, McDonald AM, Norrie JD, Carlson RV, Bridgman S: **Developing a placebo-controlled trial in surgery: issues of design, acceptability and feasibility.** *Trials* 2011, **12**:50.
7. Frobell R, Lohmander L, Roos E: **The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment.** *Contemp Clin Trials* 2007, **28**:295–302.
8. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP: **A controlled trial of arthroscopic surgery for osteoarthritis of the knee.** *N Engl J Med* 2002, **347**:81–88.
9. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt CJ, Graves SE, Staples MP, Murphy B: **A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures.** *N Engl J Med* 2009, **361**:557–568.
10. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TLN: **Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear.** *N Engl J Med* 2013, **369**:2515–2524.
11. Cullen K, Hall M, Golosinskiy A: **Ambulatory surgery in the United States, 2006.** *Nat Health Stat Rep Nat Cent Health Stat* 2009, **11**:1–28.
12. Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH, Levy BA, Mandl LA, Martin SD, Marx RG, Miniaci A, Matava MJ, Palmisano J, Reinke EK, Richardson BE, Rome BN, Safran-Norton CE, Skoniecki DJ, Solomon DH, Smith MV, Spindler KP, Stuart MJ, Wright J, Wright RW, Losina E: **Surgery versus physical therapy for a meniscal tear and osteoarthritis.** *N Engl J Med* 2013, **368**:1675–1684.
13. Herrlin S, Hållander M, Wange P, Weidenhielm L, Werner S: **Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomized trial.** *Knee Surg Sports Traumatol Arthrosc* 2007, **15**:393–401.
14. Kirkley A, Birmingham TB, Litchfield RB, Giffin R, Willits KR, Wong CJ, Feagan BG, Donner A, Griffin SH, D'Ascanio LM, Pope JE, Fowler PJ: **A randomized trial of arthroscopic surgery for osteoarthritis of the knee.** *N Engl J Med* 2008, **359**:1097–1107.
15. Englund M: **The role of the meniscus in osteoarthritis genesis.** *Rheum Dis Clin N Am* 2008, **34**:573–579.
16. Englund M, Guermazi A, Roemer FW, Aliabadi P, Yang M, Lewis CE, Torner J, Nevitt MC, Sack B, Felson DT: **Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The multicenter osteoarthritis study.** *Arthritis Rheum* 2009, **60**:831–839.
17. Englund M, Lohmander LS: **Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy.** *Arthritis Rheum* 2004, **50**:2811–2819.
18. Hare KB, Lohmander LS, Christensen R, Roos EM: **Arthroscopic partial meniscectomy in middle-aged patients with mild or no knee osteoarthritis: a protocol for a double-blind, randomized sham-controlled multi-centre trial.** *BMC Musculoskelet Disord* 2013, **14**:1.
19. Rembold CM: **Number needed to screen: development of a statistic for disease screening.** *BMJ* 1998, **317**:307–312.
20. Nelson HD, Helfand M, Woolf SH, Allan JD: **Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. preventive service task force.** *Ann Intern Med* 2002, **137**:529–541.
21. Sharp L, Cotton SC, Alexander L, Williams E, Gray NM, Reid JM: **Reasons for participation and non-participation in a randomized controlled trial: postal questionnaire surveys of women eligible for TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears).** *Clin Trials* 2006, **3**:431–442.
22. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R: **Barriers to participation in randomized controlled trials: a systematic review.** *J Clin Epidemiol* 1999, **52**:1143–1156.
23. Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, Colthart IR, Ross S, Shepherd SM, Russell D: **Factors that limit the quality, number and progress of randomized controlled trials.** *Health Technol Assess* 1999, **3**:1–143.
24. Hegedus EJ: **Physical examination tests for assessing a torn meniscus in the knee: a systematic review with meta-analysis.** *J Orthop Sports Phys Ther* 2007, **37**:541–550.
25. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT: **Incidental meniscal findings on knee MRI in middle-aged and elderly persons.** *N Engl J Med* 2008, **359**:1108–1115.
26. Frobell R, Roos EM, Roos HP, Ranstam J, Lohmander LS: **A randomized trial of treatment for acute anterior cruciate ligament tears.** *N Engl J Med* 2010, **363**:331–342.
27. Cook JA, McCulloch P, Blazeby JM, Beard DJ, Marinac-Dabic D, Sedrakyan A: **IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage.** *BMJ* 2013, **346**:f2820.

doi:10.1186/1745-6215-15-167
Cite this article as: Hare *et al.*: The challenge of recruiting patients into a placebo-controlled surgical trial. *Trials* 2014 **15**:167.