RAINE SIHVONEN

Arthroscopy for Degenerative Meniscus Tear

■

UNIVERSITY OF TAMPERE

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To Susanna and Risto

fidelity (fɪˈdɛlɪtɪ)

n, pl -ties

1. devotion to duties, obligations, etc; faithfulness

2. loyalty or devotion, as to a person or cause

3. faithfulness to one's spouse, lover, etc

4. **adherence to truth; accuracy in reporting detail**

5. (Electronics) *electronics* the degree to which the output of a system, such as an amplifier or radio, accurately reproduces the characteristics of the input signal.

(Collins English Dictionary - Complete & Unabridged 10th Edition)

CONTENTS

1   LIST OF ORIGINAL COMMUNICATIONS

The thesis is based on the following original publications (I-V). The articles are reproduced with permission from their copyright holders.

I.   Sihvonen R, Järvelä T, Aho H, Järvinen TLN: Validation of the Western Ontario Meniscal Evaluation Tool (WOMET), a meniscal pathology specific quality-of-life index, for patients with a degenerative meniscus tear. J Bone Joint Surg-Am 94:e65(1-8), 2012

II.   Sihvonen R, Paavola M, Malmivaara A, Järvinen TLN: Finnish Degenerative Meniscal Lesion Study (FIDELITY): a protocol for a randomised, placebo surgery controlled trial on the efficacy of arthroscopic partial meniscectomy for patients with degenerative meniscus injury with a novel 'RCT within-a-cohort' study design. BMJ Open. 2013 Mar 9;3(3): e002510.

III. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TLN: Arthroscopic Partial Meniscectomy vs. Sham for a Degenerative Meniscus Tear. N Engl J Med 2013;369:2513-22.

IV.   Järvinen TLN, Sihvonen R, Bhandari M, Sprague S, Malmivaara A, Paavola M, Schünemann HJ and Guyatt G: Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol 2014;Feb 19. (Epub ahead of printing)

V.   Sihvonen R and Järvinen TLN. Validity of mechanical symptoms as an indication for knee arthroscopy in patients with degenerative meniscus tear. (submitted)

The author has a significant contribution for all the papers. The author's contribution was in conceptualizing and designing the study for Papers I-III and V and in collecting and analysing the data for Papers I, III and V. The author contributed to the writing for all the papers and approved the final versions of all manuscripts.

2   ABBREVIATIONS

AAOS	The American Academy of Orthopaedic Surgeons
ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
APM	Arthroscopic partial meniscectomy
BLOKS	Boston Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
BML	Bone Marrow Lesion
DVT	Deep vein thrombosis
HRQoL	Health related quality of life
ICRS	The International Cartilage Repair Society
IKDC	International Knee Documentation Committee
ITT	Intention to treat
K-L	Kellgren and Lawrence (scale)
KOOS	Knee Injury Osteoarthritis Outcome Score
MCII	Minimal clinically important improvement
MRI	Magnetic resonance imaging
OA	Osteoarthritis
PA	Pyogenic arthritis
PASS	Patient acceptable symptom state
PE	Pulmonary embolism
PRO	Patient reported outcome
PT	Physical Therapy
QoL	Quality of life
RCT	Randomized controlled trial
VAS	Visual analogue scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WOMET	Western Ontario Meniscal Evaluation Tool
WORMS	Whole-organ magnetic resonance imaging score

3   ABSTRACT

Knee arthroscopy is the most common orthopaedic procedure with two million operations performed annually in the USA alone. Most of these surgeries are performed to treat degenerative knee disease. Degenerative knee disease is a continuum of various symptoms and clinical findings of the knee, which eventually may lead to established knee osteoarthritis (OA). In the early phase of knee disease symptoms may be very mild and sporadic. Recent recommendations stand against performing knee arthroscopy for patients with a primary diagnosis of knee OA, whereas arthroscopic partial meniscectomy (APM) is the most often performed single procedure by orthopaedic surgeons today. Most of these operations are performed on middle-aged and elderly patients to treat degenerative meniscus tear. Indications for APM include knee pain and mechanical symptoms such as catching and locking of the knee, of which the latter are considered as the universally accepted absolute indication for knee arthroscopy. High quality evidence of the efficacy of APM for degenerative meniscus tear is completely lacking and the scientific evidence supporting the validity of mechanical symptoms as an indication for knee arthroscopy is scarce. Accordingly, the aim of this study was to assess the current surgical treatment strategy for degenerative meniscus tear, namely, to assess the efficacy of APM for patients with degenerative meniscus tear and to assess if the outcome is different (better) for those reporting mechanical symptoms and finally, to assess if APM (does indeed) alleviate(s) mechanical symptoms.

This study constitutes a randomized sham-surgery controlled trial carried out using a novel RCT within a cohort design. In the trial, 146 patients aged 35 to 65 were randomly allocated to either APM or sham surgery. For the assessment of mechanical symptoms as a valid indication for APM, 765 patients in the cohort having degenerative meniscus tear were divided into those reporting mechanical symptoms preoperatively and to those reporting no such symptoms. The outcome was assessed at 12 months postoperatively using validated outcome measurements and patient satisfaction and improvement.

Although in the RCT both groups (APM and sham surgery), showed a marked improvement after surgery, no statistically significant differences between groups were observed at follow-up. The alleviation of mechanical symptoms after surgery was similar after APM compared to sham surgery. In the cohort, it was found that patients with mechanical symptoms had a more severe preoperative knee situation and poorer outcome than those without mechanical symptoms and that mechanical symptoms were not a prognostic factor for the outcome.

In conclusion, APM is not an efficient treatment modality for patients with degenerative meniscus tear and knee arthroscopy should not be performed on patients with degenerative meniscus tear.

4   TIIVISTELMÄ

Polven tähystystoimenpide on yleisin ortopedinen leikkaustoimenpide. Niitä tehdään USA:ssa n. 2 miljoonaa ja Suomessa n 30 000 vuosittain. Suurin osa toimenpiteistä tehdään sellaisten polvioireiden hoitamiseksi, jotka liittyvät polven degeneraatioon eli rappeumaan. Polven degeneraatio on jatkumo oireita ja polven muutoksia, jotka alussa saattavat olla vähäisiä ja vain ajoittaisia. Alkuvaiheessa muutoksiin kuuluvat rustopintojen rispaantuminen ja yksittäiset vauriot sekä nivelkierukan haurastuminen ja repeämät. Polven degeneraation myöhäisvaihe on polven nivelrikko. Nykyisten suositusten mukaan sellaisia polvia, joiden päädiagnoosi on nivelrikko, ei pitäisi tähystää. Polven rappeumaan liittyvän kierukkarepeämän hoito, tähystyksellinen osapoisto, on yleisin yksittäinen ortopedinen toimenpide. Yleisin syy kierukkarepeämäleikkaukseen on polvikipu, mutta on myös muita syitä, kuten polven ns. mekaaniset oireet (jumiutuminen ja lukkiutuminen). Samalla kun kipu on aina relatiivinen indikaatio kirurgiselle hoidolle, mekaanista oiretta pidetään lähes absoluuttisena indikaationa, koska mekaanisen oireen ajatellaan syntyvän kierukan repeämästä ja olevan siten hoidettavissa kierukan revenneen osan poistamisella. Korkeatasoinen tieteellinen näyttö kierukkatoimenpiteen tehosta potilaiden oireisiin kuitenkin puuttuu. Tämän tutkimuksen tavoitteena oli selvittää onko degeneratiivisen kierukkarepeämän tähystyksellinen osapoisto tehokas hoitomuoto. Lisäksi selvitettiin onko polven mekaaninen oire hyväksyttävä syy polven tähystykselle.

Tutkimus koostui satunnaistetusta lumekontrolloidusta tutkimuksesta sekä kohorttitutkimuksesta. Kontrolloidussa tutkimuksessa 146 35 – 65 vuotiasta potilasta satunnaistettiin joko kierukan osapoistoon tai lumetoimenpiteeseen. Kohorttitutkimuksessa 765 potilasta, joilla todettiin rappeumaperäinen kierukkarepeämä, jaettiin kahteen ryhmään sen mukaan oliko heillä ennen toimenpidettä polven mekaanista oireilua vai ei. Molemmissa tutkimuksen osa-alueissa leikkaushoidon tulosta arvioitiin vertaamalla ryhmiä keskenään. Tulosten arviointiin käytettiin potilaille sopivia ja validoituja mittareita sekä potilaiden tyytyväisyyttä ja arviota polvensa tilanteesta verrattuna tilanteeseen ennen tähystystä 12 kk kuluttua toimenpiteestä.

Vaikka satunnaistetussa tutkimuksessa molemmissa ryhmissä havaittiin huomattava polven tilanteen muutos parempaan toimenpiteen jälkeen, ei ryhmien välillä havaittu

tilastollisesti merkitsevää eroa millään tulosmuuttujalla arvioitaessa. Polven mekaaninen oire ei helpottanut kierukan osapoistolla enempää kuin lumetoimenpiteellä. Kohorttitutkimuksessa havaittiin, että polven lähtötilanne ja leikkaustulos ovat huonompia sellaisilla potilailla, joilla oli mekaanista oireilua, eikä mekaaninen oire ollut yksittäinen tulosta ennustava tekijä.

Tämä tutkimus osoittaa, että polven nivelkierukan tähystyksellinen osapoisto ei ole tehokkaampi kuin lumetoimenpide sellaisten potilaiden polvioireiden hoidossa, joilla on polven rappeumaan liittyvä kierukkarepeämä. Niillä potilailla, joilla todetaan mekaanista oireilua, leikkaustulos on vielä huonompi, eikä mekaanista oiretta näin ollen voida pitää indikaationa tähystykselle. Tähystystoimenpiteestä olisikin pidättäydyttävä silloin, kun polvioireen taustalla epäillään olevan rappeumaan liittyvä nivelkierukkarepeämä.

5 INTRODUCTION

 Middle-aged men and women with knee pain attributed to degenerative knee disease constitute a large group of patients referred to orthopaedic surgeons (McAlindon, Cooper et al. 1992; Katz, Solomon et al. 2000; Mantyselka, Kumpusalo et al. 2001; Jinks, Jordan et al. 2004). Degenerative knee disease is usually treated initially conservatively. However, when non-operative treatment fails, arthroscopic treatment is widely used for these patients (Cullen, Hall et al. 2009; Kim, Bosque et al. 2011). Arthroscopic treatment includes debridement (lavation, removal of loose articular cartilage fragments), treatment of cartilage lesions and, most importantly, resection (removal) of torn parts of the meniscus (Felson 2010).

Knee arthroscopy is the most common orthopaedic procedure with two million such operations performed annually in the USA alone (Cullen, Hall et al. 2009). Surgery for torn menisci covers approximately half of these operations (Hawker, Guan et al. 2008; Cullen, Hall et al. 2009; Kim, Bosque et al. 2011). The field has been in turmoil due to an exceptional scientific scrutiny of prevailing clinical practice. The initial triggers for the observed change in clinical practice were two pivotal randomized placebo (-surgery) controlled studies (RCT) showing that arthroscopic debridement or lavage was no better than a sham procedure (Bradley, Heilman et al. 2002; Moseley, O'Malley et al. 2002). These findings were soon corroborated by another study showing that arthroscopic debridement with supervised physiotherapy is no better than physiotherapy alone (Kirkley, Birmingham et al. 2008). Somewhat remarkably, this evidence also resulted in an apparent change in clinical practice, as the number of arthroscopic debridements of the knee for patients with established OA has decreased over the past decade. This evidence has also prompted the current national recommendations to opt against performing knee arthroscopy for patients with a primary diagnosis of knee OA (Conaghan, Dickson et al. 2008; Richmond, Hunter et al. 2009; Zhang, Nuki et al. 2010). However, the recommendations left an option of performing knee arthroscopy for patients with signs and symptoms of a torn meniscus (Conaghan, Dickson et al. 2008; Richmond, Hunter et al. 2009) and for patients with low-grade OA (Zhang, Nuki et al. 2010).

Given the typical difficulties in (resistance to) changing clinical practice guidelines, such a revolution might be considered unprecedented (Prasad, Cifu et al. 2012). However, a closer look actually (disappointingly) suggests that the change noted above was actually more of an illusion, as the observed decrease in the number of arthroscopic knee procedures (debridement and lavage) for patients with OA was accompanied by a simultaneous increase in the number of arthroscopies for meniscus (Hawker, Guan et al. 2008; Kim, Bosque et al. 2011). Moreover, even this *status quo* has been challenged by more recent evidence from two RCTs that cast doubts over performing meniscectomy for patients with knee OA (Herrlin, Wange et al. 2013; Katz, Brophy et al. 2013). Again, the evidence seems to be calling for a change – at least in the clinical practice (guidelines) - as the recently updated version of the recommendations by The American Academy of Orthopaedic Surgeons (AAOS) states: "We are unable to recommend for or against arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus" (Brown 2013).

But what about current clinical practice? According to our past experience from other fields of medicine (Prasad, Cifu et al. 2012), the fiercest resistance to change is to be found among clinicians. According to the most recent literature, APM is recommended by most orthopaedic surgeons for patients with knee OA, especially if there are any mechanical symptoms (i.e. catching or locking of the knee) (Conaghan, Dickson et al. 2008; Felson 2010; Krych, Bert et al. 2013; Li, Karlsson et al. 2014). Most importantly, in patients with a meniscus tear but no established knee OA, APM is virtually universally proposed as the treatment of choice (Lyman, Oh et al. 2012).

As a result, APM is currently the single most commonly performed procedure by orthopaedic surgeons (Garrett, Swiontkowski et al. 2006; Cullen, Hall et al. 2009). However, the scientific rationale for performing the procedure rests on studies that are mostly retrospective case series or cohort studies with no control group (Paxton, Stock et al. 2011), obviously prone to a high risk of bias. High quality evidence of the efficacy of APM for degenerative meniscus tear is completely lacking.

Accordingly, the aim of this project was develop and carry out a trial to assess as thoroughly as possible the efficacy of APM for patients with degenerative meniscus tear.

6 REVIEW OF THE LITERATURE

6.1 Degenerative knee disease

Degenerative knee disease is a spectrum of symptoms and joint changes affecting the knee joint, ranging from mild symptoms of cartilage defects and/or meniscal tears in relatively young patients to established knee OA in older population. The end stage, OA, is a major cause of disability among elderly people (Guillemin, Rat et al. 2011). It is an increasingly significant health concern in most countries, and according to the World Health Organization (WHO), is among the top 10 conditions in Europe with respect to burden on society (Woolf and Pfleger 2003; Lopez, Mathers et al. 2006). The diagnosis of knee OA is usually made by history and physical examination, typically in population over 50 years old (Luyten, Denti et al. 2012). Signs and symptoms suggestive of knee OA include knee pain, stiffness, joint crepitus and functional limitations. The diagnosis is ultimately made using knee radiographs, in which grade $\geq$ 2 assessed by the Kellgren and Lawrence (K-L) scale is usually considered the threshold for having the disease (Kellgren and Lawrence 1957; Felson, Niu et al. 2011). The Kellgren–Lawrence scale is a radiographic classification of the severity of knee osteoarthritis: Grade 0 denotes no abnormalities, and grade 1 minor degenerative changes (doubtful narrowing of the joint space or possible osteophytic lipping), grade 2 denotes OA (definite osteophytes and possible narrowing of joint space) and grades 3 to 4 more severe OA (Schiphof, Boers et al. 2008). However, before the radiographic or clinical findings fulfilling the criteria for knee OA (Altman, Asch et al. 1986), the signs and symptoms of a degenerative knee disease are usually present, but may be more or less elusive and sporadic, only becoming manifest under certain conditions, such as after long-term loading (Kon, Filardo et al. 2012; Luyten, Denti et al. 2012). The history of clinical recurrence of pain, discomfort in the knee and short periods of stiffness interspersed with long periods of very few symptoms suggests knee degeneration and a local problem of a mechanical nature with no systemic manifestations. (Zhang, Nevitt et al. 2011; Luyten, Denti et al. 2012) In *early* OA/degenerative knee disease, the pathologic knee findings, such as joint surface fibrillation and single or multiple cartilage defects, meniscal tears, degeneration and

extrusion of the meniscus, bone marrow lesions (BMLs), subchondral sclerosis and cysts, synovitis and presence of joint fluid are detected by magnetic resonance imaging (MRI) or knee arthroscopy (Guermazi, Niu et al. 2012; Luyten, Denti et al. 2012). The first attempt to clearly define the diagnostic criteria for a disease entity entitled "early OA" was recently made by Luyten et al. (Luyten, Denti et al. 2012) (Table 1). These criteria emphasize knee pain and one of the following findings seen at arthroscopy or MRI: chondral softening or meniscal tear.

Table 1. Criteria for early OA according to the Luyten. (Luyten, Denti et al. 2012)

Three criteria	
1 Knee pain	At least two episodes of pain for 10 days in the last year
2 Standard radiographs	Kellgren–Lawrence grade 0 or I or II (osteophytes only)
3 At least one	
Arthroscopy	ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling
MRI	At least two
	Cartilage morphology WORMS 3–6 Cartilage BLOKS grade 2 and 3 Meniscus BLOKS grade 3 and 4 BMLs WORMS 2 and 3

ICRS = The International Cartilage Repair Society

WORMS = Whole-organ magnetic resonance imaging score

BLOKS = Boston Leeds osteoarthritis knee score

BMI = Body Mass Index

6.2   Meniscus

Menisci are two semi-lunar fibrocartilagenous disks in the knee located between the femoral and tibial cartilage surfaces at both sides of the knee; lateral and medial. The

most important functions of the menisci are to increase the congruency of the tibiofemoral joint, thereby decreasing the load stress in the joint and to passively stabilize the knee (McDermott and Amis 2006). A potential contribution in aiding joint lubrication, proprioception and the nutrition of articular cartilage has also been suggested for the menisci (Seedhom, Dowson et al. 1974). The previously claimed role for the menisci as shock absorbers has lately been questioned (Andrews, Shrive et al. 2011). When normal function of the meniscus is lost either due to a tear of the meniscus and/or after surgical resection, the risk for the acceleration of the development of degenerative changes of the knee is increased (Fairbank 1948; Roos, Ostenberg et al. 2001; McDermott and Amis 2006; Englund 2009).

6.2.1   Meniscus tear

Meniscus tissue may tear due to an external force or to a degenerative process of the knee. Traditionally, meniscus tears have been classified into traumatic or degenerative based on morphology (arthroscopic or MRI-based tear characteristics) or the aetiology (injury mechanism) (Smillie 1968; Noble 1975; Metcalf and Barrett 2004).

Morphologically, meniscus tears can be classified into predominantly longitudinal and horizontal (Smillie 1968). According to the prevailing conception, longitudinal tears (vertical and bucket handle (extended vertical)), radial and flap tears usually occur in younger patients and are thus considered traumatic (Smillie 1968; Metcalf and Barrett 2004; Camanho, Hernandez et al. 2006), whereas horizontal (horizontal and complex) tears are mostly observed in older patients and are categorized as degenerative (Metcalf and Barrett 2004). The distinction between the two types of tear is often difficult and this morphological classification scheme has actually met with considerable criticism. First, it necessitates either knee arthroscopy or MRI investigation to be carried out and second, the differentiation is based on patient characteristics, not the injury mechanism; Tears in older individuals and in patients with knee OA are classified as degenerative, whereas those in young individuals as traumatic despite of the onset of the symptoms/injury mechanism.

An alternative classification of meniscus tears, based on the aetiology of the tear (patient history), also exists. There are a few clinical factors that aid in making the distinction (Larking 2010):

1) Age: There is high quality evidence from cohort studies to show that the incidence/prevalence of meniscus tears with degeneration increase with age (Curl, Krome et al. 1997; Lewandrowski, Muller et al. 1997; Englund, Guermazi et al. 2008).

2) Knee OA: High quality evidence also exists that degenerative tears (particularly horizontal tears, complex tears and degenerate menisci) are more strongly associated with the presence of OA than other tears (Bhattacharyya, Gale et al. 2003; Berthiaume, Raynauld et al. 2005; Hayes, Jamadar et al. 2005; Englund, Guermazi et al. 2009).

3) Body Mass Index (BMI): High quality evidence exists that higher BMI is strongly associated with higher prevalence of meniscal tears and these tears are more likely to be degenerative in nature (Ding, Martel-Pelletier et al. 2007; Englund, Guermazi et al. 2008).

4) Anterior Cruciate Ligament (ACL) injuries: Evidence consistent across a range of case series studies shows that 70 to 90% of meniscus tears associated with acute ACL injuries are traumatic (peripheral or longitudinal) and the proportion of degenerative tears (flap and horizontal tears) is small. Further, tears associated with intact ACL ligaments may occur secondary to pre-existing, ongoing and underlying disease processes and may only be a symptom of early degenerative disease (Poehling, Ruch et al. 1990; Meister, Indelicato et al. 2004).

5) Other knee trauma: Some evidence exists that longitudinal/bucket handle/vertical tears predominately occur due to specific injury events while horizontal tears are more likely due to degeneration (Drosos and Pozo 2004; Boks, Vroegindeweij et al. 2006).

6) Symptoms: There is some evidence to suggest that degenerative tears often occur bilaterally, in both the symptomatic and the asymptomatic knee of the same person, whereas traumatic tears are more commonly found unilaterally in the symptomatic knee (Boden, Davis et al. 1992; Zanetti, Pfirrmann et al. 2003; Boks, Vroegindeweij et al. 2006).

6.2.2   Traumatic meniscus tears

The symptoms related to a traumatic meniscus tear range from something as trivial as mild pain to haemartron and a locked knee, a complaint resulting from meniscus tissue

being caught between the articular surfaces (Allum and Jones 1986; Bansal, Deehan et al. 2002). The differentiation of symptoms due to meniscus tear *per se* and on the other hand from concomitant pathologies such as bone bruises and stretched joint capsule and ligaments is as yet unstudied. Risk factors for traumatic meniscus tears are twisting injury to the knee, ACL tear and weight bearing during trauma (Snoeker, Bakker et al. 2013). The incidence of traumatic meniscus tears is at its highest among people in their twenties and thirties (Smillie 1968). Arthroscopic meniscus repair or reinsertion is the treatment of choice for traumatic tears, if only technically feasible (Sgaglione, Steadman et al. 2003). If there is no possibility for repair, a partial meniscus resection is then recommended. If the repair is successful, the outcome of meniscus surgery is often claimed to be better than that after a resection, but rigorous evidence on this issue is scarce (Paxton, Stock et al. 2011; Xu and Zhao 2013). It has been speculated that the altered mechanical function of the knee due to a meniscus resection may eventually lead to increased loading on the chondral surfaces and to so-called Fairbank' changes (degenerative changes) seen in x-ray images. However, despite radiographic degenerative changes most of these patients are later asymptomatic and there is a discrepancy between radiographic and clinical outcome after APM of traumatic meniscal tear (Fabricant and Jokl 2007; Petty and Lubowitz 2011), although in recent years a number of imaging based studies have reduced the discrepancy between structural findings on imaging and symptoms (Hunter, Guermazi et al. 2013).

6.2.3   Degenerative meniscus tear

The risk factors for a degenerative meniscus tear are high BMI, age, male sex, work related kneeling and squatting and climbing stairs (Snoeker, Bakker et al. 2013) as well as generalized OA, knee trauma and varus alignment of the knee (Englund, Felson et al. 2011). The risk factors for degenerative meniscus pathology are mainly similar with those for knee OA (Blagojevic, Jinks et al. 2009). Most surgically treated meniscus tears – according to current estimates, as high as 80% - are degenerative in nature (Poehling, Ruch et al. 1990; Englund, Roos et al. 2001; Drosos and Pozo 2004; Metcalf and Barrett 2004; Christoforakis, Pradhan et al. 2005; Camanho, Hernandez et al. 2006). It has even been argued that - analogous to a prolapsus of an intervertebral disk - an isolated traumatic tear in a healthy meniscus does not exist as a clinical entity of its own (Weber 1994). Only if the viscoelastic properties of the meniscus tissue have deteriorated may indirect force cause a tear (Weber 1994). In this vein, in their review

article, Shelbourne and Gray proposed that an isolated meniscus tear (without an ACL tear) is almost always degenerative in nature (Shelbourne and Gray 2012). Degenerative meniscus tears are often associated with knee OA (Ding, Martel-Pelletier et al. 2007; Englund, Guermazi et al. 2008), but are also seen in patients without radiographic OA as a part of (the) degenerative knee disease (Englund, Guermazi et al. 2008; Guermazi, Niu et al. 2012; Luyten, Denti et al. 2012). Furthermore, degenerative meniscus tears have also been suggested to be associated with future knee OA and are thus apparently an early sign of knee OA (Englund, Guermazi et al. 2009). Knee pain and mechanical symptoms are the most common symptoms among patients with degenerative meniscus tear (Noble 1975; McBride, Constine et al. 1984; Dervin, Stiell et al. 2001). There is increasing evidence that degenerative meniscus tear may not be the direct cause of these symptoms (Greis, Bardana et al. 2002), but rather an innocent bystander on the path to degenerative knee disease and osteoarthritis (Englund, Roemer et al. 2012).

To summarize, acute, traumatic meniscal tears are seen in younger patients with no knee OA, usually coinciding with ligamentous injury. Degenerative tears, in turn, are seen in older patients and may or may not be related to a single traumatic incident. Although the name of the injury, the target organ, and often even the symptoms are similar in traumatic and degenerative meniscus tears, the true nature of these conditions is totally different; traumatic tears are an incident to damage to healthy tissue (Camanho, Hernandez et al. 2006) whereas degenerative tears are a part of a degenerative process culminating in knee osteoarthritis (Christoforakis, Pradhan et al. 2005; Englund, Guermazi et al. 2009).

6.3   Incidence and clinical importance of degenerative tears

Pathological meniscal findings on MRI are common among patients over 45 years of age with knee OA (Bhattacharyya, Gale et al. 2003; Englund, Guermazi et al. 2008), and even among 60% of subjects without any knee complaints (Englund, Guermazi et al. 2008). A meniscus tear is also a common finding (12% to 36%) on MRI among younger subjects under 40 years of age and even among those with no knee OA (Boden, Davis et al. 1992; Zanetti, Pfirrmann et al. 2003; Guermazi, Niu et al. 2012). Understandably, the clinical relevance of meniscus tear found on MRI has been called into question. Bhattacharyya et al. (Bhattacharyya, Gale et al. 2003) assessed the

prevalence of meniscus tear and found a tear among 86% of symptomatic patients with various degrees of knee OA and 67% among asymptomatic controls. When the subgroup of symptomatic patients was further analysed, no differences were found between those with a meniscal tear and those with no tear with respect to the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score of disability or knee pain (Bhattacharyya, Gale et al. 2003). Other studies have confirmed this lack of an association between a meniscal tear and knee symptoms, whereas a significant association has been observed between knee symptoms and degree of knee degeneration (Link, Steinbach et al. 2003; Kornaat, Bloem et al. 2006; Neogi, Felson et al. 2009; Katz, Chaisson et al. 2012). Based on the findings of a cohort of 991 subjects over 50 years of age, Englund et al. summarized the issue as follows: "Our findings suggest that meniscal damage is common among middle-aged and elderly persons, irrespective of knee symptoms, and often accompanies knee osteoarthritis" (Englund, Guermazi et al. 2008). They also have stated that: "In middle-aged and older adults, any association between meniscal damage and the development of frequent knee pain seems to be present because both pain and meniscal damage is related to OA and not because of a direct link between the two" (Englund, Niu et al. 2007). The association between meniscal tears and degeneration of the knee has lent support to the idea that, rather than being a clinical entity in its own right, a degenerative meniscal lesion could actually represent one of many features of degenerative knee disease, even in an early phase of the disease among patients with no verifiable knee OA (Englund 2004; Englund, Guermazi et al. 2009; Guermazi, Niu et al. 2012).

If a meniscal tear found on MRI in patients with degenerative knee disease seems to have very limited clinical significance, one is tempted to wonder whether it is possible for a physician to identify patients with a symptomatic meniscus tear by means of patient history, symptoms or clinical examination. Dervin et al. designed a study aimed to assess the accuracy and reliability of physicians' clinical diagnoses of unstable meniscus tear in patients with symptomatic OA (Dervin, Stiell et al. 2001). Using a standardized assessment protocol on 152 patients, the authors showed that only 60% (40% to 73%) accuracy of predicting unstable meniscal tear could be achieved. The experience of the physician had no influence on this result. The only factor in the medical history or clinical investigation that seemed to be significantly associated with the existence of a meniscal tear was a positive McMurray test (localized joint line pain or a palpable or audible and painful click related to maximal flexion and rotation of the knee). However, the interobserver repeatability of this test was reported to be only fair.

A history of mechanical symptoms, among others, was not a predictive factor for a meniscus tear (Dervin, Stiell et al. 2001). By contrast, in a recent study by Kamimura analysing the relationship between arthroscopic meniscal findings and clinical symptom, the authors found significantly higher frequencies of pain on standing and a catching sensation in patients with flap tears (Kamimura, Umehara et al. 2014). In conclusion they suggest that clinical symptoms in patients with osteoarthritis of the knee may be caused by meniscal tears, but all patients studied had knee OA and meniscal tear and comparison with those without a tear was therefore not feasible (Kamimura, Umehara et al. 2014).

In studies particularly assessing the source of knee pain, subchondral bone sclerosis, bone marrow lesion and synovitis have instead been found to be associated with knee pain (Zhang, Nevitt et al. 2011; Guermazi, Niu et al. 2012). This concurs with the classic study of neurosensory mapping of the knee by Dye et al. suggesting that the painful synovitis and capsular inflammation frequently associated with a meniscus injury may be a more important factor than a sensation arising solely from the damaged meniscus (Dye, Vaupel et al. 1998).

6.4   Arthroscopic treatment of degenerative knee

For decades arthroscopic treatment has been administered to patients with symptomatic degenerative knee disease after a failed attempt at conservative treatment. Arthroscopic debridement, lavage and meniscectomy have been suggested as the gold standard for patients with knee OA. There is a vast amount of evidence on the good outcomes of arthroscopic treatment for osteoarthritic knees – all based on uncontrolled follow-up studies (Day 2005; Figueroa, Calvo et al. 2013; Spahn, Hofmann et al. 2013; Steadman, Briggs et al. 2013). However, an increasing controversy regarding the efficacy of lavage and arthroscopic debridement has emerged after the publication of two controlled trials summarized below:

6.4.1   Controlled trials of arthroscopic treatment of knee OA

In the seminal placebo-surgery controlled trial on the efficacy of knee arthroscopy and associated debridement of knee OA, Moseley et al. randomized a total of 180 patients with osteoarthritis of the knee to either arthroscopic debridement, arthroscopic lavage,

or placebo surgery (Moseley, O'Malley et al. 2002). After two years of follow–up, all three groups displayed a statistically significant improvement, but there was no difference between these groups. In essence, the authors demonstrated that lavage or debridement were not superior to placebo treatment (skin incisions only). Both placebo and surgical interventions showed a beneficial effect on the course of symptoms. Both the 1996 published pilot study and the actual trial (Moseley, Wray et al. 1996; Moseley, O'Malley et al. 2002) was welcomed with unprecedented attention. To briefly summarize the feedback, the validity of the study was questioned on the basis of alleged methodological shortcomings, namely: inappropriate patient selection or selection bias (Chambers, Schulzer et al. 2002) and the resulting lack of generalizability, (Chambers and Schulzer 2002; Ewing and Ewing 2002; Felson and Buckwalter 2002; Jackson 2002; Johnson 2002; Fowler 2003; Gillespie 2003; Kirkley, Birmingham et al. 2008; Marx 2008; Felson 2010; Ilahi 2010), the absence of validated outcome measurements (Chambers, Schulzer et al. 2002; Kirkley, Birmingham et al. 2008; Felson 2010), and inappropriate statistical methods (Chambers and Schulzer 2002; Felson and Buckwalter 2002; Gillespie 2003). Also, the ethics of using placebo/sham surgery controls was questioned (Day 2005). The most vehement criticism of the study came in 2010 from one of the insiders of the actual trial, accusing the trial of marked selection bias resulting in misinterpretation of the trial (Ilahi 2010).

Because of the concerns about generalizability raised in the Moseley trial, a group of Canadian investigators led by Dr. Kirkley undertook a randomized trial assessing the efficacy of arthroscopy in a broader, more generalizable sample of patients with knee OA (Kirkley, Birmingham et al. 2008). Obviously prompted by the concerns mentioned above, the researchers also used validated outcome measures, multiple surgeons performing the operations, and the overall statistical design was well planned and executed. They randomly assigned 188 patients with symptomatic knee OA (with grades 2, 3, or 4 radiographic severity, as defined by the Kellgren–Lawrence scale) to either surgical lavage and arthroscopic debridement together with optimized physical and medical therapy or to physical and medical therapy alone. In total agreement with the findings of Moseley et al. (Moseley, O'Malley et al. 2002), no beneficial effect of arthroscopic debridement combined with proper conservative treatment was found during the two-year follow-up when compared with conservative treatment alone (Kirkley, Birmingham et al. 2008).

6.5   Changes in practices

It seems that the evidence yielded by those RCTs has prompted a change in clinical practice, as the number of knee arthroscopies for patients with OA has decreased quite dramatically in the past decade (Kim, Bosque et al. 2011; Potts, Harrast et al. 2012). Apart from the evidence derived from the controlled trials, (Moseley, O'Malley et al. 2002; Kirkley, Birmingham et al. 2008), another possible explanation for the decrease in the use of arthroscopy for knee OA may be a change in the coding of the diagnosis; Since 2004, Medicare no longer pays for knee arthroscopy performed to treat OA , and accordingly it has been speculated that on the basis of insurance authorization, many cases that would have had a diagnostic code for knee OA may have been coded more recently as meniscus tears because many knees with OA also have degenerative meniscus tears (Kim, Bosque et al. 2011). Numerous national organizations, including the AAOS, are currently opposed to performing knee arthroscopy on patients with a primary diagnosis of knee OA (Conaghan, Dickson et al. 2008; Weber 2009; Zhang, Nuki et al. 2010; Brown 2013). However, the AAOS and many experts still advocate arthroscopy of degenerative knees (even with established OA) for patients with a meniscus tear, particularly if these patients have 'mechanical symptoms' attributable to meniscus tear or a loose body (Stuart and Lubowitz 2006; Weber 2009; Felson 2010; Richmond 2010). Accordingly, procedures carried out to treat a degenerative meniscus tear have recently shown a steady increase (Hawker, Guan et al. 2008; Kim, Bosque et al. 2011). While the number of arthroscopic procedures performed for knee OA decreased slightly from 1996 to 2006, the total number of arthroscopic procedures performed for knee increased in the USA by nearly 50%, most of this being a result of increased number of surgeries for meniscus tear (Kim, Bosque et al. 2011). The decreased number of arthroscopies to treat osteoarthritis could be speculated to result not only from the change in diagnostic coding but also increased use of other treatment modalities, but the total number of knee arthroscopies for degenerative knee disease may not have changed (Kim, Bosque et al. 2011; Potts, Harrast et al. 2012; Buchbinder, Richards et al. 2013). According to the most recent report, for the period 2005 - 2011, it appears that the speed of the increase in the total number of meniscectomies performed has decreased, but the incidence of meniscectomies still increased 14% in that time frame (Abrams, Frank et al. 2013).

Out of nearly two million arthroscopic procedures on knees performed annually in the USA alone, half were operations for meniscus tears (Cullen, Hall et al. 2009). Most of

these patients (70 %) were over 45 years of age and the most common operation in that age group was the operation for meniscus. In England, 51,651 arthroscopies and in Ontario, Canada 17,797 were performed in 2004, mostly on non–traumatic patients; 60% of these for internal derangement of the knee and approximately 20% for OA (Hawker, Guan et al. 2008). In Finland, approximately 30,000 knee arthroscopies were carried out in 2011, almost half of these being APMs, which was the most common procedure performed by orthopaedic surgeons. The mean age of these patients was 50 years. In addition, approximately 4,000 arthroscopic knee debridements were also carried out (THL 2014).

6.6   APM for degenerative meniscus tear

The rationale for performing arthroscopic partial meniscectomy is to alleviate or even cure/treat knee symptoms and eventually knee related disability by removing torn meniscal fragments and trimming the meniscus back to a stable rim. Knee pain is the most common symptom leading to surgery, but there are also other indications, such as so-called mechanical symptoms (catching and locking sensations) (Noble 1975; McBride, Constine et al. 1984; Greis, Bardana et al. 2002; Lyman, Oh et al. 2012; Hutchinson, Moran et al. 2013). There is a myriad of studies (uncontrolled case series) suggesting that APM can work in patients with degenerative meniscus tear (Hamberg and Gillquist 1984; Rand 1985; Boe and Hansen 1986; Ogilvie-Harris and Basinski 1991; Bonamo, Kessler et al. 1992; Covall and Wasilewski 1992; Jaureguito, Elliot et al. 1995; Barrett, Treacy et al. 1998; Pearse and Craig 2003; Bin, Kim et al. 2004; Bin, Lee et al. 2008; Ozkoc, Circi et al. 2008). The outcome of surgery in these observational studies is generally good. Most patients achieve an excellent or good outcome, but despite that, substantial disability, impaired quality of life (QoL), and reduced activity levels is evident 14 weeks after APM (Roos, Roos et al. 2000). Unfortunately, as they are uncontrolled, most of these studies are associated with a high risk of bias. Further, the distinction between traumatic and degenerative meniscus tear is not always clear, although this is important information as the prognosis for degenerative tears is inferior (Englund, Roos et al. 2003; Camanho, Hernandez et al. 2006). Thus scientific studies with the highest internal validity on the effectiveness of APM for patients with degenerative meniscus injury have been completely lacking until the beginning of this century. The few published RCTs are briefly summarized below:

6.6.1 Controlled trials of APM for degenerative meniscus tear

In an open label prospective study, Biedert compared four different methods to treat an isolated and symptomatic painful grade 2 (intrasubstance) lesion of the medial meniscus (Biedert 2000). Forty patients were randomly assigned by date of birth to one of the following four treatment groups: conservative therapy (n = 12); arthroscopic suture repair with access channels (n = 10); arthroscopic minimal central resection, intrameniscal fibrin clot and suture repair (n = 7); and arthroscopic partial meniscectomy (n = 11). After 12 to 36 months' follow-up, respectively 75%, 90%, 43%, and 100% of patients in four groups had normal or nearly normal knee function assessed by the International Knee Documentation Committee (IKDC) tool (Biedert 2000).

In the first high-quality trial assessing the efficacy of APM, ninety-nine middle-aged patients with an MRI-verified degenerative medial meniscus tear and radiographic osteoarthritis (Ahlbäck grade ≤1) (K-L ≤ 3 (Petersson, Boegard et al. 1997)), mean age 56 years, were randomized to APM followed by supervised exercise therapy or supervised exercise therapy alone (Herrlin, Hallander et al. 2007; Herrlin, Wange et al. 2013). The authors found no significant difference between the groups according to any outcome instrument (Knee injury and Osteoarthritis Outcome Score (KOOS), Lysholm Knee Score, Tegner Activity Scale or knee pain) during 5-year follow-up (Herrlin, Wange et al. 2013).

Kirkley et al. compared knee arthroscopy and conservative treatment to conservative treatment alone in the treatment of knee OA (K-L 2-4), and found no difference in the outcome of treatment (relief of symptoms/pain) between the two groups (Kirkley, Birmingham et al. 2008). Of the patients in the arthroscopic surgery –group 81% also underwent meniscal resection, suggesting that besides the arthroscopic debridement, APM likewise offers no benefit for patients with knee OA.

In the pilot study by Osteras et al., 17 patients with knee pain and MRI-verified degenerative meniscus tear along with various degrees of knee OA (K-L 0-2) were randomly assigned to either exercise therapy or arthroscopic surgery (Osteras, Osteras et al. 2012). At the end of the treatment, three months after randomization, there were no differences between the two groups regarding knee pain and function. However, there was a significant difference between the two groups in that in the exercise

therapy group patients reported significantly less depression and anxiety (Osteras, Osteras et al. 2012).

In a multicentre trial involving 351 symptomatic patients (radiographic OA, K-L 0-3) 45 years of age or older with meniscal tear and evidence of mild-to-moderate OA seen in MRI, Katz et al. found no difference in the WOMAC physical-function score between surgery and postoperative physical therapy (PT) compared to standardized physical-therapy regimen alone (Katz, Brophy et al. 2013). Participants had an arthroscopic partial meniscectomy (n=161) or initial physiotherapy (n=169) with the option of surgery later. Both groups had comparable improvements in the WOMAC score over six and 12 months.

In the most recent study, Yim et al. compared APM with conservative treatment in a sample of 102 patients with knee pain and an MRI-detected degenerative horizontal tear of the posterior horn of the medial meniscus, but no radiographic OA (Yim, Seon et al. 2013). Mean age of patients was 54 years and non-operative treatment consisted of strengthening exercises. Outcomes were compared using a visual analogue scale (VAS) for pain, Lysholm knee score, Tegner activity scale, and patient subjective knee pain and satisfaction. The results showed that meniscectomy did not provide greater functional improvement than the non-operative treatment. In addition, subjective satisfaction did not differ between the two groups. In both groups there was relief from knee pain, improved knee function, and a high level of satisfaction with treatment at 2-year follow-up (Yim, Seon et al. 2013).

In these randomized trials involving patients with degenerative meniscus tear and mild to moderate knee OA or a degenerative horizontal tear of the medial meniscus in knees without OA, APM has not been shown to be effective. However, the active treatment also included chondral shavings/debridement and thus no direct conclusions on the benefit of APM *per se* can be drawn. (Herrlin, Wange et al. 2013; Katz, Brophy et al. 2013; Yim, Seon et al. 2013) Notably, in the studies by Herrlin et al. (Herrlin, Wange et al. 2013) and Katz et al. (Katz, Brophy et al. 2013), patients treated without surgery had an option to cross over to surgery and this option was used by 28% and 30% of patients respectively. This cross-over rate has also been an argument by advocates of APM to demonstrate that even if not the first-line treatment option, surgery ought to be reserved as an option for patients who fail to improve after conservative management. It is also important to note that in these studies numerous

different outcome measurement tools were used (IKDC, KOOS, WOMAC, pain on Visual Analogue Scale (VAS) and Lysholm knee score). Although most of them are tested for psychometric properties and validated for patients with meniscus tear and/or for patients with degenerative knee, little is known of the impact of the results of the different scores. However, although that issue may be theorized, all the above mentioned trials are in perfect concordance in their claim that APM has no beneficial effect.

6.7   Factors predicting the outcome of APM

A number of factors have been associated with the outcome of APM (Meredith, Losina et al. 2005; Fabricant, Rosenberger et al. 2008), the most consistent ones being cartilage degeneration (Hamberg and Gillquist 1984; Matsusue and Thomson 1996; Barrett, Treacy et al. 1998) and preoperative knee OA indicating poorer prognosis (Covall and Wasilewski 1992; Crevoisier, Munzinger et al. 2001; Fabricant, Rosenberger et al. 2008). Also, lateral meniscus tear (vs. medial meniscus tear) has been reported to be associated with poorer radiographic outcome (Chatain, Adeleine et al. 2003) after APM and lower Lysholm scores after total meniscectomy (Hede, Larsen et al. 1992). Corroborating that the overall result of APM for degenerative tear is poorer than that for traumatic tear, (Englund, Roos et al. 2003; Camanho, Hernandez et al. 2006; Salata, Gibbs et al. 2010) bone marrow edema in the same compartment as the meniscus tear and meniscal extrusion, severity of joint degeneration and meniscus root tear seen in MRI have all been identified as predictors of poor outcome (Kijowski, Woods et al. 2011). Further, female gender has been reported to be associated with poor knee function and delayed recovery after APM in some of the studies, as well as a higher rate of radiographic change than in males (Meredith, Losina et al. 2005; Fabricant and Jokl 2007; Morrissey, Goodwin et al. 2008; Rosenberger, Dhabhar et al. 2010). Conversely, the length of time between injury and surgical evaluation has not reported a prognostic association (Rosenberger, Dhabhar et al. 2010). To sum up, patients with lesser grade of articular chondral changes, no preoperative knee OA and tear on the medial meniscus are likely to have the best (anticipated) prognosis after APM. Finally, mechanical symptoms in patients with meniscus tear are considered an indication for knee arthroscopy by orthopaedic surgeons (Lyman, Oh et al. 2012; Krych, Carey et al. 2014).

6.8   Mechanical symptoms as an indication for knee arthroscopy

Although virtually every physician is familiar with the concept of 'mechanical symptoms' and it is also widely used in the literature, it has not been decisively defined. Patients with degenerative knee disease rarely have an objectively confirmable 'locked knee' (one that cannot be fully extended), but rather present with somewhat vaguer symptoms termed 'catching' and 'locking' (Noble and Erat 1980). The exact cause of this sensation is unknown, but it has been attributed to internal knee derangement (i.e., loose bodies, chondral derangement and/or meniscal tears). An indication means that there is a reason for medical intervention. One could understand that it means that the current interventions improve the prognosis in relation to no treatment at all or an alternative treatment. Mechanical symptoms of the knee (sensations of catching and locking) are currently quite universally considered an absolute indication for knee arthroscopy (Lyman, Oh et al. 2012). However, the evidence supporting such a policy is scanty. In reviewing the literature, one can identify two possible explanations for mechanical symptoms being considered an indication for knee arthroscopy in patients with degenerative knee disease (even with established knee OA). The first is simply intuition: it seems quite obvious that there is a widely-held consensus among orthopaedic surgeons that mechanical symptoms are of truly mechanistic-origin (e.g. due to an intra-articular mechanical derangement/blockage, such as a meniscal tear and thus amenable to treatment with a mechanical procedure) (Greis, Bardana et al. 2002; Stuart and Lubowitz 2006). An alternative explanation, some authors have found – mostly in retrospective studies – that mechanical symptoms are associated with good outcome after knee arthroscopy (Lotke, Lefkoe et al. 1981; Baumgaertner, Cannon et al. 1990; Ogilvie-Harris and Basinski 1991; Wouters, Bassett et al. 1992; Yang and Nisonson 1995). However, other studies (with mainly prospective study designs) have found that mechanical symptoms are not associated with either poor or good outcome of surgery (McLaren, Blokker et al. 1991; Dervin, Stiell et al. 2003; Aaron, Skolnick et al. 2006). In the RCT by Kirkley et al. no benefit was derived from surgery in the subgroup of patients with mechanical symptoms of catching or locking (Kirkley, Birmingham et al. 2008). This study is particularly pertinent to the present project as half of the patients allocated to arthroscopy had mechanical symptoms and the majority (80%) underwent partial meniscectomy. It should be noted that these findings should be interpreted with caution as the presence of a large bucket handle tear was used as an exclusion criterion in the trial. Finally, in a very recently presented *post hoc* analysis of patients enrolled in the MeTeOR trial (Katz, Brophy et al. 2013), the

improvement in mechanical symptoms was more pronounced in patients who received APM than those who received PT. However, the authors found no association between baseline mechanical symptoms and improvement in WOMAC and concluded that their data did not support the clinical teaching that frequent mechanical symptoms at baseline predict greater pain relief following APM than following PT (Katz, Wright et al. 2013).

6.9   Long-term consequences of APM

According to a recent review, radiographic signs of osteoarthritis are significant at eight to 16 years' follow-up after APM, but these changes do not necessarily develop into obvious clinical symptoms of OA (Petty and Lubowitz 2011). Radiographic results show some evidence of degenerative changes after arthroscopic partial meniscectomy in 20% to 60% of patients (Petty and Lubowitz 2011). Although several clinical follow-up studies evaluating the outcome after partial meniscectomy have been performed, no causal relationship between meniscal injury, partial meniscectomy, and OA development has been established (Ruiz, Koenig et al. 2013). This has been attributed to the fact that the effects of knee trauma itself, meniscal damage and meniscal resection, the underlying degenerative process and the risk for developing osteoarthritis cannot be distinguished from each other (Englund 2009; Katz and Martin 2009; Englund, Roemer et al. 2012). Evidence from a longer follow-up (18 to 25 years) suggests that the deterioration over time in knee-related pain and function is greater in meniscectomised subjects than in reference subjects (Roos, Bremander et al. 2008). Knee OA and the meniscus have thus an inseparable but partly controversial connection (Englund, Roemer et al. 2012).

6.10   Complications of knee arthroscopy

Although knee arthroscopy is generally considered to be a very safe procedure, it is not without complications (Salzler, Lin et al. 2013). In addition, performing arthroscopy on older patients especially may require special consideration as this group is less mobile, and often has medical comorbidities (Cullen, Hall et al. 2009; Hame, Nguyen et al. 2012). The most common serious complications associated with knee arthroscopy are pyogenic arthritis (PA), deep vein thrombosis (DVT), pulmonary embolism (PE) and death. The overall complication rate after knee arthroscopy has been reported to be

between 0.64 % and 1.6% (Bohensky, deSteiger et al. 2013; Martin, Pugely et al. 2013). In the most recent report, the complication rate after meniscectomy was found to be 2.8% (Salzler, Lin et al. 2013). Rates for PA are reported to be 0.13% to 0.4, for DVT 0.32% to 0.8%, for PE 0.05% to 0.3 and for death 0.01% to 0.03% at 90 days postoperatively (Hame, Nguyen et al. 2012; Bohensky, deSteiger et al. 2013; Martin, Pugely et al. 2013). With these numbers the annual incidence of complications of knee arthroscopy in the USA and Finland are presented in Table 2.

Table 2. Modelling of annual incidence of complications attributable to knee arthroscopy for degenerative knee based on the existing literature (Cullen, Hall et al. 2009; THL 2014).

Complications	USA 700,000 arthroscopies	Finland 15,000 arthroscopies
All	3,500 to 10,710	76 to 230
Pyogenic arthritis	840 to 2800	19 to 60
Deep venous thrombosis	2,240 to 5,600	48 to 120
Pulmonary embolism	350 to 2,100	7 to 45
Deaths	70 to 210	2 to 5

6.11   Non- surgical treatment of patients with degenerative meniscal tears

Beside five RCTs focusing on APM for patients with knee OA (showing little or no benefit with surgery and thus preferring for non-surgical management) (Kirkley, Birmingham et al. 2008; Osteras, Osteras et al. 2012; Herrlin, Wange et al. 2013; Katz, Brophy et al. 2013; Yim, Seon et al. 2013) there are comparative and cohort studies and case series suggesting that medial knee pain and symptoms attributed to degenerative meniscus tear might be treated successfully by non- surgical/conservative treatment

modalities. In 1970, Lequesne et al. (Lequesne, Bensasson et al. 1970), already reported the successful treatment of the joint line pain (provoked by McMurray manoeuvre) of thirty patients with juxtameniscal cortisone infiltration. All but one had permanent relief from symptoms. More recently, Andro et al. (Andro, Dubrana et al. 2011) compared surgery (arthroscopy including joint lavage and partial meniscectomy in case of meniscal lesion) and medical treatment (joint rest, simple analgesia, infiltration and/or weight-loss diet) in a nonrandomized prospective cohort study in patients over 45 years of age with medial knee pain (almost all with meniscal tear). They found no significant differences between the groups as regards the outcome and 80 percent of patients in both groups were satisfied six months after the treatment. In their prospective study, Rimington et al. (Rimington, Mallik et al. 2009) found that patients improved after initial conservative treatment, although half of them chose to be operated on afterwards when surgery was offered. Stensrud et al. (Stensrud, Roos et al. 2012) reported results of the first 20 conservatively treated patients included in their ongoing randomized controlled trial and found that the majority of patients improved and none of the patients did undergo surgery. Within the past few years other prospective case-series have also reported excellent and good recovery after exercise therapy in patients with degenerative meniscus tear (Neogi, Kumar et al. 2013; Rathleff, Cavallius et al. 2013). Similarly, Lim et al. demonstrated that non-surgical treatment provided symptom relief in most patients with the degenerative posterior root tear of the medial meniscus and functional improvements in a short-term follow-up in their retrospective review of 30 patients. Conservative treatment modalities are thus preferred for non-traumatic knee pain in all patients over 40 years of age with femorotibial joint space narrowing in spite of meniscal tear detected in MRI (Beaufils, Hulet et al. 2009).

None of these studies are randomized trials and thus may include bias. However, whether the outcome after a non-invasive treatment is biased by fluctuation of the symptoms, regression to the mean, placebo, or a combination of these (or a result of subjects participating in a study) it does not lessen the value of the resulting recommendation for non-surgical treatment. As non-surgical treatment seldom has significant side-effects or complications compared to surgical treatment and at the same time has many positive effects on subjects´ general health, one may question why the evidence should be so rigorous. Nevertheless, whether expensive supervised therapy is more appreciated than basically free home-based exercise is important, if cost-effectiveness is taken into account. However, there is a lack of evidence as to

which type of conservative treatment or exercise therapy works best or even if conservative treatment modalities work better than so-called watchful waiting as no controlled trials exist for patients with degenerative meniscus tear (Stensrud, Roos et al. 2012). A home exercise programme or supervised outpatient PT following arthroscopic partial meniscectomy resulted in comparable outcomes in studies by Jokl et al. and Goodwin et al (Jokl, Stull et al. 1989; Goodwin, Morrissey et al. 2003). For patients with knee OA, according to a recent systematic review of randomized controlled trials, (Juhl, Christensen et al. 2014) exercise programmes should focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. The programme should also be supervised and carried out three times a week focusing on one aim at a time for the best result. (Juhl, Christensen et al. 2014) These results remain the same regardless of age, sex, BMI, radiographic status, or baseline pain and thus may also be generalized for patients with degenerative meniscus tear. Finally, a study found active treatment and exercise to be better than placebo (subtherapeutic ultrasound to the knee) when treating knee OA (Deyle, Henderson et al. 2000).

6.12   Summary of the most recent literature on APM of degenerative meniscus tear

According to the most recent literature and especially the results of studies with the highest quality of evidence (low risk of bias), knee arthroscopy is not beneficial in the treatment of patients with degenerative meniscus tear with concomitant knee OA. There are two further distinct indications for knee arthroscopy of a degenerative knee. First, APM for patients with symptomatic meniscus tear and no OA and second, APM for patients with mechanical symptoms with or without knee OA. However, the rationale for the current treatment strategy is not supported by high-quality evidence. And finally, research on the efficacy of APM is completely lacking.

6.13   Assessing efficacy

RCT is considered the gold standard of research design in terms of methodological rigour (internal validity). Ideally, a well-designed RCT should not only have high internal validity but also preferably high external validity (generalizability) (Farrokhyar, Karanicolas et al. 2010). However, realistically, such a 'wish' is an obvious paradox, as

there is an almost inevitable trade-off between internal and external validity. In essence, the purpose of a true efficacy (or explanatory) trial is to demonstrate that an intervention can work theoretically under optimal conditions ('best-case scenario') (Haynes 1999). An effectiveness (or pragmatic) trial, in turn, is aimed at testing how an intervention works under usual practice circumstances, and for this reason has a high external validity (albeit restricted to the patient case-mix, which may be different in different health care settings and change according to current treatment practices), but the internal validity is usually lower (Roland and Torgerson 1998; Bombardier and Maetzel 1999; Farrokhyar, Karanicolas et al. 2010). The existing evidence, coming from more or less pragmatic trials, questions the effectiveness of APM. However, there is still a possibility that APM can be demonstrated to be efficacious– i.e., APM could prove to be effective for an ideal patient group under ideal treatment circumstances.

As noted above, the methodological choices of a study do matter. When evaluating the results of case series there is always considerable uncertainty as to whether the intervention has a causal relationship with the results. Only randomized controlled studies are capable of preventing confounding at baseline and making the intervention and control arms comparable both for documented and undocumented determinants of outcome. The factors which may affect the results of APM – at the time of the intervention or during follow-up – are the natural course of symptoms, regression to the mean, and the placebo effect. The act of randomization, when successful, can control for the first two of these but not the last one, the placebo effect. All these determinants should be controlled for to be able to truly assess the efficacy of surgical intervention per se.

6.13.1   Natural course of the disease

The natural course of disease could explain even 10 to 20% of recovery demonstrated in studies of acute or chronic pain (Krogsboll, Hrobjartsson et al. 2009). The fluctuating course of symptoms in degenerative knee disease has been demonstrated in several studies (Hawker, Stewart et al. 2008; Neogi, Nevitt et al. 2010; Soni, Kiran et al. 2012). The fluctuating level of pain in degenerative knee disease is particularly associated with a change in bone marrow lesions´ (BML) size (Dore, Quinn et al. 2010). It is generally known that people tend to seek medical help at the time of prevalent pain, and according to the evidence cited above; an improvement in the symptoms is to be anticipated even without an intervention.

6.13.2 Regression to the mean

A more complicated version of the phenomenon goes by the name "regression to the mean". In non-controlled trials, the regression toward the mean is overlooked as the populations studied tend to represent extremes (i.e. most symptomatic subjects) (Fitzmaurice 2000). Bland and Altman (Bland and Altman 1994) have succinctly summarized the issue as follows: "If subjects with extreme values of the measurement are measured again, we will observe that the mean of the extreme group is now closer to the mean of the whole population - that is, it is reduced. This should not be interpreted as showing the effect of the treatment. Even if subjects are not treated the measurements will go down".

6.13.3 Placebo

Given the obvious risk for bias from an un-blinded trial of surgery versus conservative treatment - particularly acknowledging the potential of surgery to produce powerful placebo effects - it has been assumed that it is doubtful that a rigorous trial of surgery can be conducted without a sham-surgery control, particularly when the primary outcome is pain, patient-reported improvement, or quality of life (Moerman and Jonas 2002; Zhang, Robertson et al. 2008; Doherty and Dieppe 2009). The findings from meta-analysis by Zhang et al. (Zhang, Robertson et al. 2008) indicates that placebo is effective in the treatment of knee OA. Placebo (compared to no-treatment) seems to have effect particularly for pain, function, stiffness and most of all for the physician's assessment of improvement (Zhang, Robertson et al. 2008). Effect for placebo of total improvement in chronic pain has been claimed to be as much as 25% according to another meta-analysis (Krogsboll, Hrobjartsson et al. 2009). In essence, this means that the observed improvement of a medical intervention may actually be attributable to a placebo effect rather than any alteration in the pathological processes involved (Moseley, O'Malley et al. 2002; Buchbinder, Osborne et al. 2009; Kallmes, Comstock et al. 2009; Landorf, Morrow et al. 2013) . Further, surgical interventions have been reported to be associated with a more pronounced non-specific/placebo effects than conservative treatment modalities (Meissner, Fassler et al. 2013).

Optimal blinding of both the patient and the researcher is an obvious asset of the placebo/sham-surgical model: patients are purportedly biased towards favourable outcomes after surgical intervention because they want to believe that they chose the

correct option for their care. This 'leap of faith' is believed to be greater in surgery than in conservative trials, in which the perceived and real risks of the intervention may be more subtle, less severe and do not involve the pain and risks of invasive procedures (Zhang, Robertson et al. 2008). Equally importantly, sham surgery is ideal for minimizing researcher-bias through true blinding of the outcome assessor (Farrokhyar, Karanicolas et al. 2010). And finally, a sham-surgery model most likely diminishes the potential cross-over to surgery arm of the trial.
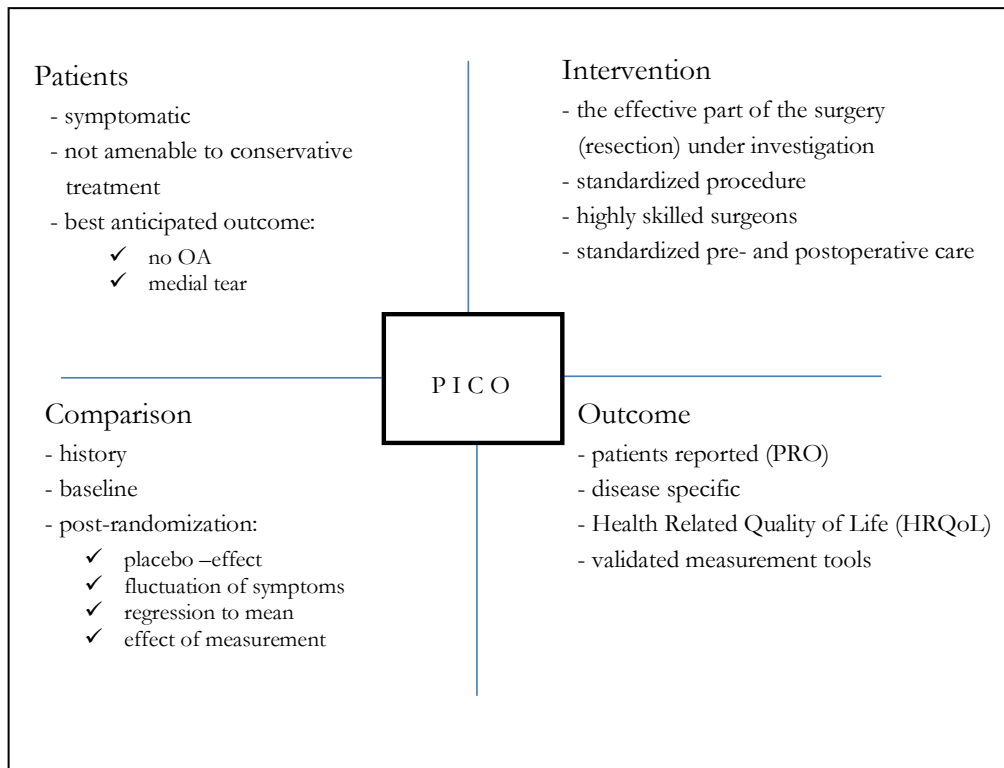
All the above mentioned facts speak strongly for the use of a control group to adequately study the true effect of medical (surgical) intervention, particularly when dealing with degenerative complaints. Without controlling for the natural course of symptoms, the regression to the mean and the placebo effect it is not possible to extract the true treatment effect of surgery *per se*.

6.14 The birth of the FIDELITY project

After a careful review of the literature, it became amply apparent, that the true efficacy of APM in patients with knee pain purportedly due to a degenerative meniscus tear, needs to be studied rigorously. For this purpose, the following study design was devised, identifying the gaps in the existing knowledge that required to be bridged to be able to successfully carry out the trial. This initiative resulted in the realization that the FIDELITY project would require the following two articles to be completed: a study protocol that would focus specifically on the scientific justification for using a sham-surgery control (ethical justification) and a separate article focusing on the assessment of the psychometric properties of a disease-specific, heath-related quality-of-life instrument (Western Ontario Meniscal Evaluation Tool, WOMET). During the course of the trial, two additional spin-offs, namely a study describing the execution of the blinded data interpretation and the assessment of the validity of mechanical symptoms as an indication for knee arthroscopy, were identified as requiring our attention. The rationale for the chosen P.I.C.O. model (Patient, Intervention, Comparison and Outcome) of the FIDELITY trial is presented in Figure 1. Accordingly, the inclusion criteria were chosen to address those with the best anticipated outcome based on the literature, the only effective part of the procedure was studied (meniscus resection), a comparison group was formed to capture all pre

and post randomization confounding factors and the outcome was assessed using a disease specific, validated outcome. (Figure 1)

Figure 1. P.I.C.O. model of the FIDELITY trial

Patients
 - symptomatic
 - not amenable to conservative
   treatment
 - best anticipated outcome:
   ✓ no OA
   ✓ medial tear

Intervention
 - the effective part of the surgery
   (resection) under investigation
 - standardized procedure
 - highly skilled surgeons
 - standardized pre- and postoperative care

P I C O

Comparison
 - history
 - baseline
 - post-randomization:
   ✓ placebo –effect
   ✓ fluctuation of symptoms
   ✓ regression to mean
   ✓ effect of measurement

Outcome
 - patients reported (PRO)
 - disease specific
 - Health Related Quality of Life (HRQoL)
 - validated measurement tools

6.15 Interpretation bias

Although guides on the reporting of randomized trials and protocols for trials are available, these initiatives focus on the provision of accurate data, whereas researchers have paid relatively little attention and provided even fewer suggestions for safeguards for the risk of misleading data interpretation (Moher, Hopewell et al. 2010; Chan, Tetzlaff et al. 2013). The concept "interpretive bias" was first introduced in 1996 by Gotzsche (Gotzsche 1996). He proposed that the authors of clinical trials should write two manuscripts, one assuming that treatment A is experimental and treatment B is control, and another article assuming the opposite (that treatment B is experimental

and A is control). He suggested that both manuscripts be completed and approved by the authors before the randomization code is broken. Another attempt at minimizing the interpretative bias was introduced in the reporting of the Study to Prospectively Evaluate Reamed Intramedullary Nails In Tibial Fractures (SPRINT) trial (Bhandari, Guyatt et al. 2008). The writing committee of the trial was once again presented with an analysis of the results as treatment A and compared it with treatment B. Rather than writing two manuscripts, they discussed and reached agreement on how they would interpret the results if treatment A proved to be reamed nailing and treatment B proved to be unreamed nailing. They recorded their decisions in the "Minutes of the Blinded Review of the Data" document that was approved by all members of the Committee (Bhandari, Guyatt et al. 2008). Interpretation of data, a vitally important part of conducting research (Kaptchuk 2003), is never totally objective and is therefore vulnerable to prior convictions, wishful thinking and conflict of interest. Presentations of results can be so profoundly misleading that the clinical message is the reverse of what should be conveyed (Gotzsche 1996; Kaptchuk 2003). Thus, effort should be made to minimize the interpretation bias.

6.16   Measuring the outcome

To be able to measure the treatment effect of a medical intervention, a validated outcome measure is a prerequisite. In essence, we should be convinced that the measurement tool does what we suppose it to do and that the results are as near to the truth as possible. Further, the outcome measure should be disease-specific and also measure health-related quality of life (HRQoL) (Guyatt, Feeny et al. 1993; Irrgang and Anderson 2002). A measurement tool should therefore quantify and measure not only impairments and disabilities such as pain and function, but also the individual's quality of life. Health-related quality of life refers to the physical, psychological and social domains of health that are influenced by an individual's experiences, beliefs, expectations and perceptions. (Irrgang and Anderson 2002) As most outcome tools are initially developed in English-speaking countries, there is need for proper translations but also a cross-cultural adaptation of the tool before using it in the target language and environment. (Guillemin, Bombardier et al. 1993; Beaton, Bombardier et al. 2000) Finally, any tool should be tested and approved for psychometric properties to be deemed a valid measurement tool for the specific purpose. Usually the validating process includes the assessment of test-retest reliability, internal consistency, content

validity (floor and ceiling effects), criterion and construct validity and responsiveness. (Irrgang and Anderson 2002) However, simply conducting a validation process does not necessarily guarantee that the tool is appropriate.

6.17   Measurement tools for knee disorders

Numerous instruments have been developed to assess the outcomes of various treatments for different knee complaints. Most of the earlier instruments were more or less general and were not based on the patient's perspective (Marx 2003; Garratt, Brealey et al. 2004). However, with improved understanding of the complexity of knee pathology, we have witnessed a recent upsurge in attempts to develop more disease-specific, valid instruments for the assessment of knee complaints, also incorporating the patients´ views on the outcome (Scott and Garrood 2000; Garratt, Brealey et al. 2004). Of the knee outcome measurement tools available, the Lysholm knee score and the IKDC have been specifically validated for patients with meniscal injury (Briggs, Kocher et al. 2006; Crawford, Briggs et al. 2007). KOOS was developed initially for assessing pain, symptoms, activities of daily living, function and knee-related quality of life in young and middle-aged subjects with ACL injury, meniscus injury, or posttraumatic osteoarthritis, (Roos, Roos et al. 1998) and has also been validated for patients with various knee injuries, including meniscal injury (Salavati, Mazaheri et al. 2008). For patients with OA, the most often used measurement tool is the WOMAC, which includes in the 42 items of KOOS (Bellamy, Buchanan et al. 1988). In two separate tests, IKDC has been reported to show better performance on all measurement properties than KOOS or WOMAC in patients with meniscal tears (Tanner, Dainty et al. 2007; van de Graaf, Wolterbeek et al. 2014).

In addition, The Western Ontario Meniscal Evaluation Tool (WOMET), the only disease-specific quality of life (QoL) index to be initially designed and validated for patients with meniscal pathology was introduced 2007 (Kirkley, Griffin et al. 2007). The WOMET has also been demonstrated to measure most of the symptoms important to patients with meniscal tear (Tanner, Dainty et al. 2007). However, the validation process of WOMET was done using mostly patients with a traumatic meniscal tear (Kirkley, Griffin et al. 2007).

Regarding the properties of measurement tools used in previous trials assessing the outcome of arthroscopic procedures for patients with degenerative meniscus tear

(IKDC, Lysholm, KOOS, WOMAC and knee pain), none of these has been specifically validated for the specific patient group with degenerative meniscus tear. As is known, there are considerable differences between traumatic and degenerative meniscus tears (aetiology, patient's age, history and co-morbid conditions), but there may also be differences between degenerative meniscus tear and knee osteoarthritis. Accordingly, the psychometric properties of an outcome instrument should be tested separately for patients with degenerative meniscus tear to ensure that the outcome measure used is valid for this particular patient population. This is especially important when evaluating the treatment effects of degenerative diseases as they are typically only quantifiable through patient-reported subjective outcomes (PROs) (Copay, Subach et al. 2007).

Accordingly, one aim of this study was to translate WOMET into Finnish and assess the psychometric properties for patients with degenerative meniscus tear.

7 AIMS OF THE STUDY

The overall aim of the present study was to investigate the rationale of the current surgical treatment strategy (arthroscopic partial meniscectomy) for patients with degenerative meniscus tears.

The specific aims of the study were as follows (Roman numerals refer to the original publications):

I.   To assess the psychometric properties of the Western Ontario Meniscal Evaluation Tool (WOMET) for patients with degenerative knee disease (specifically for patients with degenerative meniscus tear).

II.   To design a study to assess the efficacy of arthroscopic partial meniscectomy for patients with degenerative meniscus tear and to argue the methodological decisions.

III. To assess the efficacy of arthroscopic partial meniscectomy for patients with degenerative meniscus tear.

IV.   To assess the feasibility (and utility) of the blinded interpretation of study results.

V.   To assess the validity of mechanical symptoms as an indication for knee arthroscopy.

8 PATIENTS AND METHODS

8.1 Patients

The study sample consisted of 1,124 patients treated from January 2007 to January 2012 (two patients withdrew from the FIDELITY trial and also forbade all data collection, leaving 521 women and 601 men, mean age 52 years, range 19 to 81). All patients had an arthroscopically verified meniscus tear and no obvious traumatic onset of symptoms. All patients in the study were treated surgically (either APM with or without additional arthroscopic procedure or sham surgery). Data was collected prospectively and the follow-up was done by questionnaires posted to participants at two, six and twelve months postoperatively. The findings at the time of arthroscopy were registered by means of a structured form. The study includes two separate samples. First, patients eligible for the FIDELITY trial at five orthopaedic institutions in Finland (Helsinki University Hospital, Hatanpää Hospital, Jyväskylä Central Hospital, Kuopio University Hospital and Turku University Hospital) formed the RCT sample (RCT, n=170). Second, all patients over 18 years of age who underwent knee arthroscopy and arthroscopic partial meniscectomy at a single orthopaedic institution (Hatanpää Hospital, Tampere, Finland) during 2007 and 2011 constitute the pragmatic cohort (cohort, n=954). The flow chart of patients is shown in Figure 2 and baseline characteristics in Table 3.

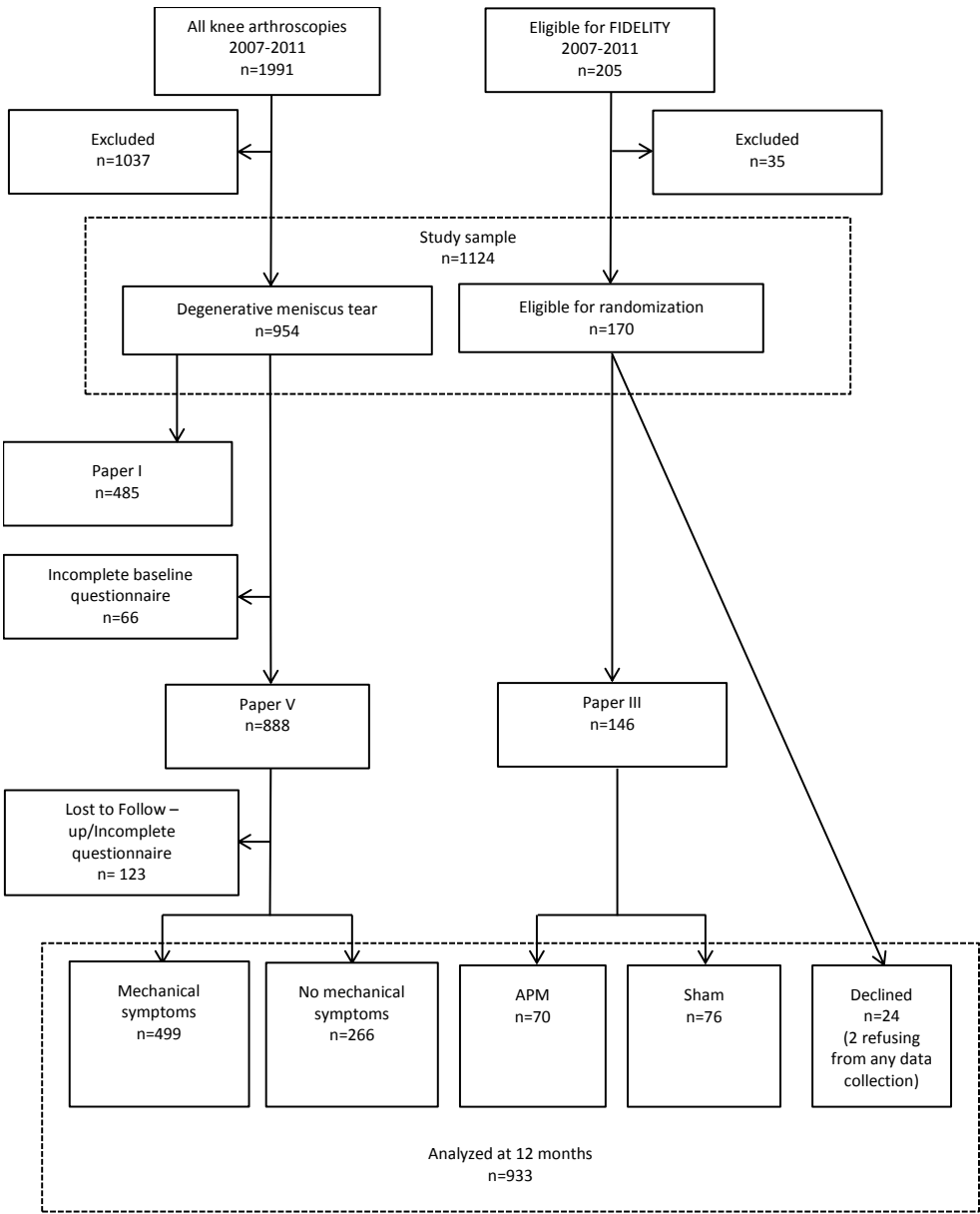**Figure 2. Flow chart of the study patients.**

Table 3. Baseline characteristics of analyzed patients in the study*

Characteristics	Cohort					RCT		
	All	Mechanical symptoms		Procedure		Groups		
	(n=765)	No (n=266)	Yes (n=499)	APM alone (n=408)	APM + additional (n=357)	APM (n=70)	Sham (n=76)	Declined (n=22)
Age - yr	53 ± 12	52 ± 12	53 ± 12	53 ± 11	52 ± 12	52 ± 7	52 ± 7	49 ± 8
Body – Mass Index†	27.5 ± 4.2	27.4 ± 4.2	27.6 ± 4.2	28.0 ± 4.0	27.1 ± 4.3	26.9 ± 4.0	27.9 ± 4.0	27.9 ± 5.5
Female Sex - no. (%)	352 (46.0)	99 (37.2)	253 (50.7)	181 (44.4)	171 (47.9)	28 (40.0)	29 (38.2)	12 (54.5)
Duration of knee pain – mo, median (range)	12 (0.5 to 528)	11.5 (0.5 to 420)	12.0 (0.5 to 528)	12 (0.5 to 420)	12 (0.5 to 528)	10 (3-50)	10 (3-47)	10 (4 to 48)
Radiological OA - no. (%)‡	149 (24.2)	39 (18.2)	110 (27.4)	66 (20.8)	83 (27.9)	0	0	0
WOMET score§	46.4 ± 19.1	54.9 ± 17.4	41.8 ± 18.5	43.9 ± 18.7	48.5 ± 19.3	56.4 ± 17.3	52.8 ± 18.1	43.4 ± 17.2
Lysholm score¶	51.9 ± 17.5	62.1 ± 14.6	46.4 ± 16.4	51.2 ± 18.0	52.6 ± 16.9	60.2 ± 14.7	60.1 ± 14.6	55.7 ± 13.9
NRS‖	4.5 ± 1.9	4.8 ± 1.8	4.3 ± 1.9	4.4 ± 1.9	4.5 ± 1.8	5.2 ± 1.6	5.0 ± 1.8	4.0 ± 1.4

* Values are means ± SD unless stated otherwise.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Radiographic evidence of osteoarthritis was considered present if the Kellgren–Lawrence grade was 2 or higher. Images of 150 of the 765 subjects were not available in the community-based, pragmatic sample because of missing radiographs.

§ The Western Ontario Meniscal Evaluation Tool (WOMET). WOMET contains sixteen items addressing three domains: nine items addressing physical symptoms; four items addressing disabilities due to sports, recreation, work and lifestyle and three items addressing emotions. The percentage of normal score is used, and accordingly, 100 (%) represents the best possible score and 0 (%) represents the worst possible score

¶ In the cohort, the Lysholm knee score was missing, and not imputed, from 7 patients with no mechanical symptoms, 21 without mechanical symptoms, 16 with APM alone and 12 with APM and additional procedure.

‖ Numerical rating scale (NRS; 0 to 10), where 10 represents a completely normal knee and 0 denotes an extremely bad knee. Value was missing, and not imputed, from 5 patients without mechanical symptoms, 2 with APM alone and 3 with APM and additional procedure.

8.1.1 Paper I

For the assessment of the psychometric properties of the WOMET score a subgroup of 485 patients (mean age 53 years, range 18 to 81; 217 females and 268 males) of the cohort treated between 2007 and 2009 were analysed. All patients proceeding to reoperation during six-month follow-up were excluded.

8.1.2 Paper III

For the assessment of the efficacy of APM 146 patients aged 35 to 65 years with knee pain (> 3 months) unresponsive to conventional conservative treatment (by general practitioners/orthopaedic surgeons before referral to an orthopaedic clinic) and clinical findings consistent with medial meniscus tear (pain on the medial joint line of the knee and pain provoked by palpation or compression (forced flexion) of the medial tibiofemoral joint line or a positive McMurray sign) were randomized and analysed 12 months after surgery (70 assigned to APM and 76 to sham surgery). All patients had MRI and arthroscopically verified tear in the medial meniscus. Patients with clinical (Altman, Asch et al. 1986) or radiographic (K-L grade ≥ 2) (Kellgren and Lawrence 1957) knee OA were excluded. The mean age of the patients was 52 years, range, 35 to 65 years; 57 females, and 89 males. Of the eligible patients 24 declined to participate and thus were excluded prior to randomization, but were also followed up. Two of those who declined did not want to participate at all, leaving 22 patients to be further analysed. The mean age of the 22 declining patients was 49 years, range 35 to 60; 12 female and 10 male.

8.1.3 Paper V

For the assessment of mechanical symptoms as an indication for knee arthroscopy, all patients in the cohort who had acceptably completed the baseline questionnaires were included (888 patients treated between 2007 and 2011). Of those, 765 (86%) patients (mean age 53, range 19 to 81; 352 females and 413 males) were analysed at 12-month follow-up. In addition, a sub-group of 325 patients of the 765 patients (mean age 53 years, range from 19 to 81; 152 females and 173 males) who also responded to the question about mechanical symptoms at two and six months postoperatively provided information on the possible fluctuation/alleviation of these symptoms. Finally, 146

patients from the FIDELITY RCT were also analysed according to mechanical symptoms.

8.2   Outcomes

WOMET (Papers I, III and V)

WOMET is a disease-specific tool designed to evaluate health related quality of life (HRQoL) in patients with meniscal pathology (Kirkley, Griffin et al. 2007). WOMET contains 16 items addressing three domains; nine items for domains of physical symptoms, four for domains of disabilities due to sports, recreation, work and lifestyle, and three for emotions domain. Each of the WOMET items was given a visual analogue scale (100-mm lines anchored at the ends). For the sake of simplicity, the score is usually converted to percentage of normal, in which zero (0) denotes the worst possible situation and 100 the best possible situation (Kirkley, Griffin et al. 2007). Patients occasionally fail to answer all questions of the questionnaire. If there were 1-3 items missing, we substituted the missing value(s) (in Paper V) with the average value for the answered items according to protocol described previously for the WOMAC (Bellamy, Buchanan et al. 1988; Bellamy 1996), a similar outcome tool for established for knee OA.

Lysholm knee score (Papers I and III)

The Lysholm knee score is an 8-item questionnaire designed to evaluate knee function and symptoms of daily living in patients with anterior ligament insufficiency (Lysholm and Gillquist 1982). It has later been adjusted and validated for the evaluation of patients with meniscal injuries. (Tegner and Lysholm 1985; Briggs, Kocher et al. 2006).

Knee pain (Paper III)

Knee pain was assessed on an 11-point scale ranging from 0 (no pain) to 10 (extreme pain) both after exercise and at rest during the previous week (Downie, Leatham et al. 1978).

15D (Papers I and III)

15D, a generic health-related quality-of-life instrument including 15 dimensions and scored on a scale of 0 (death) to 1 (full health) (Sintonen 2001). The responsiveness, reliability and validity of 15D have been thoroughly established and it has been used extensively in clinical and health care research (Bowling 2004; Moock and Kohlmann 2008).

Numerical rating scale (NRS) (Papers I and V)

For the self-assessment of the knee, patients were asked the following question: "How do you rank your knee at the moment on a scale of 0-10, 10 representing a completely normal knee and 0 denoting an extremely bad knee?" This scale has been validated for patients with knee and hip OA (Ornetti, Dougados et al. 2011). The advantage of this single question is its simplicity and the ease with which it can be administered (Marx 2003).

Patient satisfaction (Papers III and V)

The patients' global assessment of satisfaction with their knee was elicited using the following question: "How satisfied are you with your knee at present?" on a 5-point Likert scale. As before, the responses "Very satisfied" or "Satisfied" were categorized as satisfied, while responses "Neither satisfied nor dissatisfied", "Dissatisfied" and "Very dissatisfied" were categorized as dissatisfied patients (Salaffi, Stancati et al. 2004; Hamilton, Lane et al. 2013).

Global impression of change (Papers I, III and V)

Patients' opinions on the success of arthroscopy were assessed using a standard global impression of change (PGIC) question as follows: "How do you rate your knee now, 12 months after arthroscopy?" on a 5-point Likert -scale. Similarly as for satisfaction, the responses "Much better" and "Better" were considered improved patients, while responses "Unchanged", "Worse" or "Much worse" were deemed not improved.

Mechanical symptoms (Papers III and V)

The presence of mechanical symptoms was assessed using the locking domain of the Lysholm knee score (Tegner and Lysholm 1985) with a minor modification (expansion) to be a patient-administered question. Briefly, the patients were asked to choose one of the five response options that best reflected the status of their knee: i) no locking or catching, ii) catching sensations but no locking, iii) occasional locking, iv) frequent locking, or v) locked at present.

Willingness to repeat the operation (Paper III)

Patients were asked in the 6-month follow-up questionnaire about their willingness to undergo reoperation due to their current symptoms. Only after the clinical examination had been carried out by an orthopaedic surgeon blind to the initial treatment, and if the clinical signs indicative of/consistent with a meniscal tear was found, was the allocation unsealed and the patient offered reoperation.

8.3 Methods

8.3.1 Paper I

Before being used in, the WOMET questionnaire was translated according to the principles of the MAPI Research Institute. (Acquadro, Conway et al. 2004) Briefly, the original English-language version of the questionnaire (found as a supplementary) was first translated into the target language by two orthopaedic surgeons independently of each other. Then a consensus version of these two versions was drafted under the supervision of the director of the translation process. This version then underwent backtranslation into English by a bilingual orthopaedic surgeon. Finally, at a meeting of all three abovementioned translators (orthopaedic surgeons), an English-language professional, and the director of the translation process, the final version in the target language was produce. The practicality (ease of use and unambiguity) of the translated questionnaire was confirmed by subjecting it to pilot testing on thirty individuals (hospital nurses). However, no formal feedback from this pilot testing was collected, nor any other cross-cultural adaptation or written reports of the process made and no native English speaking authors were involved (Beaton, Bombardier et al. 2000).

For the assessment of the psychometric properties of WOMET, the reliability (test-retest repeatability), internal consistency, content validity, criterion validity and responsiveness were evaluated. The follow-up for the analysis of responsiveness was done at six months postoperatively. From the 485 patients, two subgroups of patients were formed: 100 patients for the assessment of criterion validity and the remaining 385 patients for all other psychometric testing of WOMET (including a subgroup of 40 patients for test-retest repeatability). Six hypotheses (constructs) were developed by consensus and were tested, including five hypotheses for convergent evidence of construct validity and one hypothesis for discriminate evidence of construct validity. The five convergent hypotheses were chosen to reflect the general condition of the knee, possible impairments, pain and symptoms/findings associated with early osteoarthritis (morning stiffness and chondral lesions observed at the time of arthroscopy). The process and statistical methods used to assess the psychometric properties of WOMET are summarized in Table 4.

8.3.2   Paper II

A protocol of a sham-surgery controlled trial assessing the efficacy of APM was designed and described to address some of the problems related to both the efficacy and effectiveness of RCTs and concerns related the previous sham controlled trial of knee arthroscopy (Moseley, O'Malley et al. 2002). Also, a novel 'RCT within-a-cohort' study design was introduced. And finally, some ethical concerns for the use of the sham surgery control were thoroughly discussed.

8.3.3   Paper III

A parallel group (1:1), multicentre, randomized and sham-surgery controlled trial to assess the efficacy of APM in patients with degenerative medial meniscus tear was conducted. During the diagnostic arthroscopic procedure, if a patient was confirmed to be eligible for the trial, the surgeon asked a research nurse to open an envelope containing the study-group assignment (arthroscopic partial meniscectomy or sham

Table 4. A process of validating the WOMET

	Question	Statistical method
Reliability	Can we rely on the WOMET and the consistency of the results it yields?	
Test-retest repeatability	Does the WOMET provide the same result on repeated assessments?	Agreement of repeated tests, CVrms*
Internal consistency	Do all items of the WOMET assess the same phenomenon?	Cronbach alpha
Validity	Does the WOMET adequately measure health-related quality of life in patients with a degenerative meniscus tear?	
Content validity	Does the WOMET cover all symptoms commonly experienced by patients with a degenerative meniscus tear?	Floor and ceiling effects
Criterion validity	Are the results of the WOMET comparable to a "gold standard"?	Correlation to Lysholm and 15-D
Construct validity	Does the WOMET follow the theory it is based on?	Five hypotheses for convergent validity and one for discriminate
Responsiveness	Does the WOMET score change over time or in response to treatment?	Effect size, Standardized response mean

*CVrms= root-mean-square coefficient of variation

surgery) and reveal it to the surgeon; the assignment was not revealed to the patient. The randomization sequence involved stratification according to study site, age (35 to 50 or 51 to 65 years of age), sex, and the absence or presence of minor degenerative changes on a radiograph (Kellgren–Lawrence grade 0 or 1, respectively). The trial was designed to ascertain the superiority of APM over sham surgery at 12 months with three primary outcomes (Lysholm knee score, WOMET score and knee pain after exercise). Patients, data collectors, the data analyst and manuscript writers were blind to treatment assignments.

8.3.4   Paper IV

The literature search concerning interpretation bias was conducted and the feasibility and effectiveness of a specific approach to avoid (reduce) misleading data interpretation were tested using the FIDELITY data as our pilot data.

8.3.5   Paper V

A pragmatic prospective cohort study was conducted. The presence of mechanical symptoms was elicited preoperatively with a standardized questionnaire. For the analyses, the patients were stratified into two groups according to their preoperative self-report of the presence of mechanical symptoms (no symptoms vs. mechanical symptoms) and the outcomes of these two groups were compared after 12-month follow-up. Additionally, patients from the RCT (FIDELITY) were analysed to assess whether the outcome after APM was better than that after sham surgery for patients with mechanical symptoms, and if these symptoms could be alleviated by APM.

8.4   Statistical methods

Baseline characteristics were analysed by descriptive statistics. The preoperative scores and patients´ ages demonstrated normal distribution and mean values ± SD or range was used to describe them. The medians and range or means and 95% confidence intervals (95%CI) were used for not normally distributed scores and postoperative scores. Student's t-test and nonparametric test were used to compare continuous variables (normally distributed and not normally distributed respectively) between the groups, and Fisher's exact test was used with binomial and categorical variables. Missing values were not imputed (with the exception of 1-3 missing values of the individual WOMET score in Paper V). Statistical analyses were performed using SPSS (version 11.5 or later, SPSS Inc, Chicago, Illinois/IBM corp. Armonk, New York). A P value of 0.05 was considered to indicate statistical significance.

8.4.1   Paper I

The median values were used for the postoperative values as the distribution was not normal. Student's t-test was used for 2-group comparisons of preoperative WOMET scores. Spearman's correlation coefficient (r) was used to assess associations between WOMET and two other scales as Lysholm and 15-D were not normally distributed. Mann-Whitney test was used to compare two postoperative WOMET scores.

8.4.2   Paper III

For the primary analysis, the change in the scores (mean with 95% confidence intervals) from baseline to 12 months was compared between the two study groups. This analysis was also carried out after adjusting for the baseline score and the stratifying variables at randomization. Secondary analyses included comparisons between groups in the change in 15D score and knee pain at rest; and of the frequencies of patients reporting satisfaction; subjective improvement; reoperation; serious adverse events; or whose allocation was unsealed at 12 months. The analyses of the primary outcomes were also carried out at two and six months. As knee OA has been associated with poorer outcome after knee arthroscopy, the only pre-specified subgroup analysis was performed stratifying patients according to the extent of radiographic degenerative changes (K-L 0 [no degeneration] vs. K-L 1 [minor degenerative changes]).   For one post hoc analysis patients were also stratified according to the onset of symptoms (gradual or suddenly). All statistical analyses were performed on an intention-to–treat (ITT) basis; no per protocol analysis was performed as the frequency of crossover was low (5%).

8.4.3   Paper V

For the primary analysis, group comparisons were made according to the percentage of satisfied patients at 12-month follow-up. For the secondary analyses, the mean WOMET score and the change in the WOMET score from baseline to 12-month follow-up, percentage of improved patients and the mean Numerical Rating Score (NRS) were compared between the groups. Further, an analysis of covariance was carried out with the change in WOMET score implemented as dependent variable and mechanical symptoms, sex and radiological OA (no vs. yes) as independent variables,

and baseline WOMET score as a covariate. The success of knee arthroscopy in alleviating mechanical symptoms was also calculated. Finally, the prognostic significance of baseline characteristics (clinical, radiographic and arthroscopic findings) for postoperative patient satisfaction and alleviation of mechanical symptoms after arthroscopy was analysed using logistic-regression analysis.

8.5   Interventions

Arthroscopic partial meniscectomy

Arthroscopic examination of the knee was performed using standard anterolateral and anteromedial portals with a 4-mm arthroscope. The surgeon evaluated the medial, lateral and patellofemoral joint compartments, graded the articular lesions and meniscus lesion(s). Following diagnostic arthroscopy, the procedures deemed necessary by the operating surgeon were carried out in the pragmatic cohort. During the arthroscopic partial meniscectomy, the damaged and loose parts of the meniscus were removed with arthroscopic instruments (a mechanized shaver and meniscal punches) until solid meniscal tissue was reached. The joint was then irrigated and evacuated. In the RCT trial those allocated to APM no other procedure but an APM was done.

Sham surgery (Paper III)

For the sham surgery, a standard arthroscopic partial meniscectomy was simulated. To mimic the sensations and sounds of an authentic arthroscopic partial meniscectomy, the surgeon asked for all instruments, manipulated the knee as if an arthroscopic partial meniscectomy was being performed, pushed a mechanized shaver (without the blade) firmly against the patella (outside the knee), and used suction. The patient was also kept in the operating theatre for the amount of time required to perform an actual arthroscopic partial meniscectomy.

9 RESULTS

The baseline characteristics of the patients of the cohort (also stratified by the procedure: APM alone or APM with additional chondral procedure and by mechanical symptoms: no or yes) and those in the RCT (allocated to APM or sham-surgery or declined) are presented in Table 2. The results of patients at 12 months according to percentage of satisfied and improved patients, WOMET score, the change (improvement) in WOMET score, Lysholm knee score and NRS (Numerical Rating Scale) are presented in Table 5. Some unpublished results are included.

9.1   Paper I

The mean WOMET score ±SD was 53 ± 17 in the first and 53 ± 18 in the second assignment for those patients (37 out of 40 analysed) included in the repeatability analysis. The values of two repeated scores were within acceptable limits as defined by Bland and Altman (95% of differences (were) less than two standard deviations). (Bland and Altman 1986) There was also acceptable (Cronbach's α >0.70)(Kane 1997) internal consistency for the preoperative overall WOMET score, for the domains of physical symptoms, for the domains of sports/recreation/work/lifestyle and for the domains of emotions (Cronbach's α = .917, .890, .749 and .824 respectively). Cronbach's alpha was also acceptable for the overall WOMET scores of patients with meniscus tear without radiographic osteoarthritis (α =.913) and for the patients with radiographic osteoarthritis (α=.931). The overall WOMET score, the three domains and all sixteen items had acceptable floor and ceiling effects (<30%).

There was a significant correlation between the WOMET score and the Lysholm knee score (r = 0.558, p < 0.001). A significant although weak correlation was also found between the overall WOMET score and the overall 15-D scale (r = 0.311, p = 0.002).

Table 5. The outcome of the analyzed patients at 12 months after surgery*

| | Cohort | | | | | RCT | | |
| | All | Mechanical symptoms | | Procedure | | Groups | | |
Characteristics	(n=765)	No (n=266)	Yes (n=499)	APM alone (n=408)	APM + additional (n=357)	APM (n=70)	Sham (n=76)	Declined (n=22)
Satisfied patients	65.8 (503)	75.2 (200)	60.7 (303)	66.7 (272)	64.7 (231)	77.1 (54)	69.7 (53)	72.2 (13)
Improved patients	82.7 (627)	88.9 (233)	79.4 (394)	83.0 (336)	82.4 (291)	88.6 (62)	82.9 (63)	100 (16)
WOMET score†	72 (70 to 74)	79 (76 to 82)	68 (66 to 71)	73 (71 to 76)	71 (68 to 74)	81 (76 to 86)	80 (75 to 85)	85 (78 to 92)
Change in WOMET score	26 (24 to 27)	24 (21 to 27)	27 (24 to 29)	25 (22 to 27)	27 (25 to 29)	25 (20 to 29)	27 (22 to 32)	41 (32 to 51)
Lysholm score	75 (73 to 76)	82 (79 to 84)	71 (70 to 73)	75 (73 to 77)	75 (73 to 77)	82 (78 to 86)	83 (80 to 87)	86 (80 to 92)
NRS‡	6.9 (6.7 to 7.1)	7.3 (7.1 to 7.6)	6.7 (6.5 to 6.9)	7.0 (6.8 to 7.2)	6.9 (6.6 to 7.1)	7.4 (6.9 to 7.9)	7.5 (7.1 to 7.8)	6.6 (7.0 to 7.7)

* Values are percentages (number) for satisfied and improved patients and means with 95% Confidence Interval for scores. Values was missing at 12 month, and not imputed, as follows: in the cohort, improvement from 7, Lysholm from 23 and NRS from 9 patients, In RCT lysholm from 1 in APM group and WOMET from 3 and Lysholm from 4 from those declined.

† The Western Ontario Meniscal Evaluation Tool (WOMET). WOMET contains sixteen items addressing three domains: nine items addressing physical symptoms; four items addressing disabilities due to sports, recreation, work and lifestyle and three items addressing emotions. The percentage of normal score is used, and accordingly, 100 (%) represents the best possible score and 0 (%) represents the worst possible score.

‡ NRS denotes Numerical rating scale (0-10, 10 for the best possible score).

All five convergent hypotheses were significant and the one discriminate showed no significant difference (to ascertain that there was no accidental correlation).

Of the 385 patients, 323 (84%) returned the six-month follow-up questionnaire acceptably completed. The median preoperative and postoperative WOMET scores were 44 (range 6 to 97) and 77 (range 0 to 100) respectively. There was a large overall effect size (1.17) and a large overall standardized response mean (0.90) for the WOMET score. Also, when compared with the patients' global impression of knee function, the observed mean change in the WOMET score was greater for patients reporting that the knee was better or much better after the operation (31 ± 21) than for patients reporting that the knee was the same or worse (23 ± 16) (p < 0.001).

9.2   Paper II

A protocol for a randomised placebo surgery controlled trial to assess the efficacy of APM in patients with degenerative meniscus tear was presented. Some of the methodological issues that were crucial to the successful execution of a controlled surgical trial, particularly with respect to minimising bias and maximising the internal and external validity, were discussed. Finally, the ethical issues concerning the use of sham surgery model were discussed.

9.3   Paper III

Of the 170 eligible subjects who fulfilled all criteria, 24 declined to participate. Accordingly, a total of 146 patients underwent randomization; 70 were assigned to receive APM and 76 placebo surgery. The baseline characteristics and arthroscopic findings of the groups were similar. The patients who declined to participate were also similar to those assigned to randomization with respect to age, sex, and body mass index (BMI), and all underwent knee arthroscopy and partial meniscectomy. There was no loss to follow–up.

Whereas both treatment groups showed significant improvement in the three primary outcome measures from baseline to 12 months, there were no significant between-group differences in the change from baseline to 12 months in any of these measures (Lysholm knee score, mean difference, -1.6; 95% confidence interval, −7.2 to 4.0),

WOMET score (-2.5; −9.2 to 4.1) or knee pain after exercise (-0.1; −0.9 to 0.7). These results were not materially changed after adjusting for the baseline scores and the stratifying variables at randomization. Also, there was no statistically significant difference between the groups according to the change in scores at two or six months postoperatively.

Secondary and other outcomes

No significant between-group differences were found in any of the secondary outcomes, the frequency of reoperations or serious adverse events. Of patients in the APM group 77% compared to 79% (p=0.205) in the sham-surgery group reported satisfaction, 89% vs. 83% (p=0.230) reported improvement and respectively 93% vs. 96% (p=0.315) would choose to be operated on again if asked to make the decision again. One patient in the APM group had knee infection four months after surgery. Two patients in the APM group and five patients in the sham surgery groups (p=0.256) reported persistent symptoms postoperatively that were sufficiently severe to necessitate unblinding (average eight months after index operation) and subsequent reoperation. Patients in the sham group were not significantly more likely than patients in the APM group to guess that they had undergone a sham procedure (47% vs. 38% respectively, P=0.39). Also, in the pre-specified sub-group analysis, no between-group differences were found in the primary outcomes at 12 months when study groups were stratified according to the radiographic grading (Interaction P values from 0.388 to 0.824) nor in the *post hoc* analysis according to the onset of symptoms (sudden vs. gradual).

9.4   Paper IV

Blinded data interpretation may decrease the frequency of misleading data interpretation. Widespread adoption of blinded data interpretation would be greatly facilitated were it added to the minimum set of recommendations outlining proper conduct of randomized controlled trials (e.g. the Consolidated Standards of Reporting Trials (CONSORT) statement).

9.5   Paper V

Preoperatively, 266 (35%) patients reported no (presence of) mechanical symptoms while 499 (65%) reported the presence of mechanical symptoms. In those patients with preoperative mechanical symptoms there was a statistically significant overrepresentation of women (p<0.001), higher prevalence of radiographic OA (p=0.013), and lower preoperative WOMET score (p<0.001) and NRS score (p<0.001) than in those reporting no preoperative mechanical symptoms. No other baseline differences were observed between the two groups. The findings at arthroscopy confirmed the higher prevalence of chondral degeneration and lateral meniscus tears in the patients with preoperative mechanical symptoms. No difference was found between the two groups in the surgical procedures performed.

At the primary outcome assessment point (12 months postoperatively), 75% of patients reporting no preoperative mechanical symptoms were satisfied compared to 61% of those reporting mechanical symptoms (p<0.001). Accordingly, patients reporting no preoperative mechanical symptoms achieved a higher functional status in the WOMET score (mean score 79 vs. 68, p<0.001), and a higher proportion of them considered their knee to be improved after surgery (89% vs. 79%, p=0.001) and gave a higher overall rating of their knee (mean value 7.4 vs. 6.7, p<0.001) than did those with preoperative mechanical symptoms. No difference was observed between the two groups in mean arthroscopy-induced improvements in the WOMET score (mean score 24 vs. 27, p=0.172) nor statistical significant difference was observed between the two groups in percentage of satisfied patients, WOMET score, percentage of those considering their knee improved or NRS score after adjusting for the differences in baseline characteristics between the two groups.

Of the 499 patients reporting mechanical symptoms preoperatively, 231 (46%) reported that symptoms persisted 12 months after surgery. Accordingly, the success rate of arthroscopic surgery in alleviating mechanical symptoms was 54%. Moreover, of those with no mechanical symptoms before arthroscopy (n=266), 32 (12%) reported mechanical symptoms at the 12-month follow-up point. Multivariate logistic regression analysis showed that the preoperative WOMET score was the only baseline characteristic significantly associated with postoperative satisfaction and alleviation of preoperative mechanical symptoms.

Finally, in the other sample (FIDELITY –RCT, n=146) no statistical significance difference according to any outcome measurement was found at 12 months

postoperatively between the groups (APM vs. sham) in those 69 (32 in APM and 37 in sham group) patients with preoperative mechanical symptoms. Of patients undergoing APM 75% (23/32) were satisfied vs. 73% (27/37) of patients after sham surgery (p=0.566). The corresponding percentages of patients reporting improvement were 84% and 85% (p=0.535). There was no statistical significant difference between these two groups according to presence of mechanical symptoms during follow-up. (Table 6)

Table 6. **Proportion (number) of patients reporting mechanical symptoms at follow-up (of those patients having preoperative mechanical symptoms). P value for the difference between APM and sham surgery (Fisher's exact test).**

Follow-up	FIDELITY -RCT			Cohort	
	APM (n=32)	Sham (n=37)	P value	Subgroup (n=213)	All (n=499)
2 mo	43.8 (14)	45.9 (17)	0.524	51.2 (109)	
6 mo	37.5 (12)	24.3 (9)	0.178	50.7 (108)	
12 mo	31.2 (10)	27.0 (10)	0.451	46.9 (100)	46.3 (231)

10 SUMMARY OF RESULTS

I   The psychometric properties of the Western Ontario Meniscal Evaluation Tool (WOMET) for patients with degenerative knee disease were found to be acceptable.

II   A protocol for a randomised placebo surgery controlled trial to assess the efficacy of APM in patients with degenerative meniscus tear was presented.

III   APM was found to be no better than sham surgery in the treatment of degenerative meniscus tear.

IV   Blinded interpretation of the study results was found to be capable to diminish interpretation bias.

V   Mechanical symptoms were found to be associated with poor outcome after APM. APM was found to be no better than sham surgery in the treatment of degenerative meniscus tear in the subgroup of patients reporting mechanical symptoms preoperatively. Finally, APM did not alleviate mechanical symptoms compared to sham surgery, thus the validity of using this criterion as an indication for surgery was questioned.

11   DISCUSSION

11.1   Statement of principal findings

This prospective, randomized trial, complemented with data from a prospectively collected cohort, showed that APM is not superior to sham surgery in the treatment of patients with symptoms (considered to be) attributable to a degenerative meniscus tear. In addition, the findings of this study seriously challenge the current wisdom regarding the clinical significance of mechanical symptoms. In essence, it was found that preoperative mechanical symptoms were associated with more symptomatic knees and poor outcome of arthroscopic surgery. Further, surgery could seldom cure – or even alleviate - mechanical symptoms. To summarize, the principal findings of this project seriously question the validity of the current indications for knee arthroscopy of patients with a degenerative knee disease (degenerative meniscus tear with or without mechanical symptoms).

As arthroscopic knee surgery is high volume surgery with great direct and indirect costs to patients and society in general, it is extremely important to study the effect and burden of such treatment. This project is a natural continuum of high quality randomized trials to assess the efficacy of knee arthroscopic surgery for degenerative knee. The first two sham-controlled trials by Moseley et al. and Bradley et al. in 2002 (Bradley, Heilman et al. 2002; Moseley, O'Malley et al. 2002) quite convincingly demonstrated that debridement or lavage has no effect on knee symptoms in patients with established knee OA. These seminal trials were followed six years later by another trial assessing the effectiveness of arthroscopic knee debridement on patients' symptoms (Kirkley, Birmingham et al. 2008). The results of this trial were in total agreement with the earlier ones: arthroscopic treatment (debridement and/or meniscus resection) did not prove beneficial for those patients with knee OA. These trials prompted a change in the prevailing consensus, suggesting that arthroscopy is not beneficial for patients with a primary diagnosis of knee OA (Weber 2009). However, for one reason or another, the total number of knee arthroscopies for degenerative knees still increased (Hawker, Guan et al. 2008). A marked shift in the indication for arthroscopy in patients with degenerative knee disease was also evidenced (Hawker,

Guan et al. 2008; Kim, Bosque et al. 2011). Instead of debridements for knee osteoarthritis, the number of partial meniscectomies increased, especially for middle-aged and elderly patients (Hawker, Guan et al. 2008; Dearing and Brenkel 2010; Kim, Bosque et al. 2011). Not until the publication of two additional trials of APM for patients with knee OA (Herrlin, Wange et al. 2013; Katz, Brophy et al. 2013), were doubts regarding the efficacy of APM for those with knee OA raised (Brown 2013). When this evidence was coupled with the growing knowledge about the true nature of degenerative meniscus tear - frequently an asymptomatic finding on MRI and a part of the degenerative knee process in general - a shadow of doubt was cast over performing APM for degenerative meniscus tear (Englund, Niu et al. 2007; Englund, Guermazi et al. 2008; Englund, Guermazi et al. 2009; Guermazi, Niu et al. 2012). Despite the evidence, clinical practice shows no change, as APM was performed as often in 2011 as in 2005 (most of the procedures being carried out on middle-aged and elderly patients) (Abrams, Frank et al. 2013). Further, almost two thirds of orthopaedic surgeons still consider arthroscopy indicated even in patients with osteoarthritic knee (Mayr, Rueschenschmidt et al. 2013; Li, Karlsson et al. 2014). The reason for this evidence-practice gap can only be speculated

Our results complement earlier scientific evidence regarding the outcome of knee arthroscopy for patients with degenerative knee disease. They are in perfect agreement with previous high quality evidence in the field. At present arthroscopic surgery for degenerative knee disease may be the most rigorously studied intervention in all orthopaedic surgery: there are seven high-quality randomized trials and they all convincingly tell the same story. Most importantly, this kind of high-quality evidence is not contradicted by contrasting evidence, as no study has reported even a slightly opposing trend (of suggesting that APM provides a clinically meaningful benefit).

Acknowledging that scientific evidence does not support the prevailing practice of carrying out knee arthroscopy for patients with *symptomatic* degenerative knee disease/meniscus tear (knee pain), the presence of mechanical symptoms (sensations of knee locking or catching) remain the only rationale/indication for the procedure. In fact, according to a recent survey in the USA, knee arthroscopy for patients with mechanical symptoms is considered almost mandatory (Lyman, Oh et al. 2012).

According to the presence of preoperative mechanical symptoms, our findings suggests that reported mechanical symptoms are associated with poor knee situation

and poorer outcome after APM compared to that of those patients with no mechanical symptoms. Finally, knee arthroscopy (arthroscopic partial meniscectomy) was no better than sham surgery in alleviating sensations of catching or locking.

Taken together arthroscopy for patients with degenerative knee disease should no longer be reimbursed because of the direct costs of such surgery and the indirect costs of lost work and disability, and of course the risk of surgical complications.

11.2   Strengths of the study

The main strength of this entire effort to study the efficacy (and effectiveness) of arthroscopic knee surgery in patients with degenerative knee pain is the use of a sham (placebo) controlled randomized study design complemented with validated outcome measures. The RCT-within-a-cohort design naturally further increases the potential for the correct assessment of the generalizability of the results achieved.

11.2.1   Study design

RCT is the only way to assess the causality between the intervention and outcome as other factors potentially influencing the outcome (i.e. potential confounders) are controlled for in this design. Those factors potentially confounding the results of a study on degenerative knee disease are the characteristics of the patients, the natural fluctuating course of symptoms and regression to the mean. Besides these, it is widely agreed that controlling for the placebo effect is a critical aspect of experimental design in any clinical research (Hrobjartsson and Gotzsche 2004; Dowrick and Bhandari 2012). The use of sham surgery design not only accomplished this, but also ensured optimal blinding of both the patients and outcome assessors as well as a possibly diminished the number of patients opting for cross-over to surgical treatment. Bias in the interpretation and reporting of the results was also diminished by both registration of the study before it was actually launched, writing a protocol paper and, finally, by writing and developing two interpretations of the results on the basis of a blinded review of the primary outcome data. One methodological choice that proved successful was postponing the randomization to the operation suite. By so doing, we managed to completely eliminate the chance that any eligible patient giving informed consent would decline to participate in the trial after being randomized. Even though

our 'RCT within-a-cohort' design provides an opportunity to follow up these patients (those declining), too, the elimination of post-randomization withdrawal obviously minimized the risk of bias in terms of the comparability of the study groups at baseline. We also succeeded in minimizing the number of patients who declined to participate and no patients were lost to follow-up, both obviously increasing the internal validity of our trial.

For the other studies (Papers I and V, to test the outcome tool and to assess the prognostic significance of mechanical symptoms) a cohort study was used. Cohort studies are claimed to be a most powerful method to obtain quantitative evidence (Bryant, Willits et al. 2009) on the prognostic factors (Moons, Royston et al. 2009).

11.2.2   Sample size

The discussion on the adequacy of the sample size of any given study/trial seems never-ending (Norman, Monteiro et al. 2012). The primary purpose of using statistical tests is to minimize the probability of a type II error, in which it is erroneously concluded that there are no clinically important differences between groups when such disparity actually exists. An often neglected fact is that once a study has been carried out (i.e. the results are already at hand), there is little merit in estimating the statistical power of a study, as the power is then appropriately indicated by the confidence intervals of the results (Goodman and Berlin 1994).

Norman et al. (Norman, Monteiro et al. 2012) recently introduced a thought-provoking point of view to the debate on study power by submitting that prior statistical calculations for the sample size are no more accurate than estimates from historical data. After a relatively thorough discussion of the flaws and merits of two alternative approaches, the authors proposed that a standard, 'off-the-peg' sample size of 64 per group would be just as valid an estimate as one would obtain by more traditional, 'made-to-measure' sample size calculations (Norman, Monteiro et al. 2012).

In the FIDELITY trial, 'made-to-measure' calculations provided a range of required sample size estimates of between 40 and 54 participants per group (depending on the outcome measure) to have 80% power to show a clinically meaningful advantage of APM over placebo. Balancing between the adequacy of study power (recognizing the

potential threat/uncertainties related to dropout and uneven randomization) and the concerns of ethical acceptability, a target sample size of 70 patients per group was set.

11.2.3   Outcome measures

A validated outcome measurement tool is naturally the basis and also a prerequisite of any clinical study. To increase both internal and external validity, the used measurement tools should measure what they are intended to measure and also give as reliable results as possible.

The measurement tools used in this project were chosen (with the objective) to cover all aspects of degenerative knee disease as extensively as possible. WOMET, as a disease-specific health related quality of life (HRQoL) instrument, is specific for this patient population and has been reported to measure those symptoms most important to patients (Tanner, Dainty et al. 2007). The Lysholm knee score, in turn, as a more general knee assessment tool (although also validated for meniscus injury) provided values that were more easily comparable to those of earlier studies, as the tool has been so widely used in the past. As for the assessment of knee pain (the hallmark symptom of patients with degenerative knee disease), tested method was used (Downie, Leatham et al. 1978). For the purpose of gathering information to help health authorities to compare treatments between different health problems, the general health quality assessment instrument (15D) was used.

Choosing the optimal outcome instruments for a given research problem is a challenge, but unfortunately the difficulties do not usually stop there. Patient-reported outcomes (PROs) usually contain different items/questions and the responses to these are calculated to give a total score. In Lysholm and WOMET the score is something between 0 and 100, where 100 is the best possible score. In RCTs, the intervention effect is usually determined by comparing the different treatment groups according to the change in score or the score at final follow-up. With large samples, small differences in mean score can be declared "statistically significant", even though they may be of little clinical significance to the patient (Fortin, Stucki et al. 1995). Rather, the proper interpretations should be that such change is unlikely to be caused by chance (Copay, Subach et al. 2007). But how can we convey information regarding the response to therapy (here, knee arthroscopy) in such a way that we are able to truly comprehend it? One is faced with such questions as to how much of a change in self-

reported levels are the minimal clinically important improvement (MCII) and does the observed change in the score reflect an improvement meaningful to the patient (Copay, Subach et al. 2007; Dworkin, Turk et al. 2008)? For example, is a 20-point change from 40 to 60 better than from 60 to 80? Or a 30-point improvement from 40 to 70 better than a 20-point improvement from 60 to 80, as in the former the final score is still lower than in the latter? According to an earlier study (Tubach, Dougados et al. 2006), feeling good matters more to the patients than feeling better. In scientific terminology, satisfaction (PASS, patient acceptable symptomatic state) or final level of used score seems more important than improvement (MCII, minimal clinically important improvement) i.e. the change in score. Accordingly, the knowledge of MCII for PROs in a particular patient population is believed to facilitate comparison of the results of different studies, the understanding of the clinical importance of the results of a given intervention, and the calculation of the sample sizes. In that case if the outcome of a treatment is presented simply by the proportions of improved or satisfied patients (knowledge gathered direct from the patients), we can avoid converting the patient's perspective into a score and then back to the abovementioned proportion. Accordingly, addition to the continuous variables (measurement tools), we used above mentioned dichotomizing variables. On the other hand, if we used only dichotomizing variables, we would miss information gathered with continuous measurements. Finally, dichotomizing continuous variables has its own issues (Streiner 2002).

11.2.4   Follow up

The length for adequate follow-up after any medical intervention is always debatable. Two-year follow-up has traditionally been considered the minimum in the orthopaedic literature. However, be it also noted here that such arguments have usually been associated with reconstructive surgeries, which undoubtedly take longer to showcase the full potential recovery. Regarding APM, it has been reported that it can take up to six months postoperatively to obtain the full benefit from APM (Roos, Roos et al. 2000; Herrlin, Hallander et al. 2007). However, more sustained relief of symptoms seems to be confounded by eventual progression of the underlying degenerative process (Englund, Guermazi et al. 2009). Accordingly, to be able to showcase the potential efficacy of APM on pain and quality of life while minimizing various types of confounding and modifying factors (e.g. non-retention/loss to follow-up and

progression of knee OA), we chose a 12-month time point as our time point of primary interest. This follow–up time period (12 months) also seems appropriate for our cohort study of assessing the clinical significance of mechanical symptoms, as the potential benefits of an arthroscopic procedure on mechanical symptoms should be evident very soon after the surgery.

11.3   Generalizability of the study findings

Generalizability (external validity) of the results of a clinical trial is just as important as rigorous execution (high internal validity) with respect to the impact of the findings on health care. Generalizability reflects the usefulness of the study results and their adoption to clinical practice. The main factor in assessing the generalizability is the characteristics of the patients (inclusion and exclusion criteria) as well as the chosen intervention. If the internal validity of a study is as high as possible, as it often is in explanatory trials (and the result as near the "truth" as possible), but there still is a lack of generalizability, the study is useless for purposes of facilitating clinical decision-making. In the more pragmatic trials (effectiveness trials), where ordinary patients are studied, the generalizability is often high, but the information on the true efficacy is less obvious. Our solution to solve this dilemma contains two crucial decisions. First, the rationale for carrying out a true efficacy (explanatory) randomized trial was not to address whether APM works in ordinary practice on ordinary patients, but rather to demonstrate whether APM *can work* under optimal conditions ('best-case scenario'). In essence, we were trying to find out if the treatment exerts a biological effect in a research setting under ideal and controlled conditions. If APM was to be effective, then more pragmatic trials would be warranted to study whether APM works in ordinary practice, and, most importantly, if treating patients with knee arthroscopy is worth it (cost–effectiveness). Second, we prospectively collected all patients at one institute to comprise a cohort outside the RCT. The aim of collecting this cohort was threefold, first to verify that our inclusion criteria were correct and second to obtain information on the effectiveness of the APM in pragmatic environment, and finally to assess the prognostic factors related the outcome after APM, namely the mechanical symptoms.

11.3.1 Randomized trial

The patients recruited into the RCT were thus carefully selected to obtain as homogeneous a sample as possible and particular attention was paid to their optimal treatment. The factors most consistently found to predict a poor outcome after APM in patients with degenerative meniscus injury are advanced knee OA and chondral damage (Meredith, Losina et al. 2005; Fabricant, Rosenberger et al. 2008; Salata, Gibbs et al. 2010). Also, lateral meniscectomy has been identified as a predictor of poorer prognosis rather than medial meniscectomy (Chatain, Adeleine et al. 2003; Salata, Gibbs et al. 2010). Accordingly, to obtain a sample with 'optimal anticipatable response to APM', we chose to recruit patients with a stable knee, no or minimal degenerative changes and an isolated, degenerative tear of the medial meniscus. Also, the study design (efficacy trial with very strict eligibility criteria) reduces any concerns related to enrolment bias, as the results would not materially change whether or not we managed to recruit all patients eligible for the study. If only, for an example, 20% of patients eligible were enrolled, they would still represent a best-case scenario. A study by Katz et al. (Katz, Brophy et al. 2013) succeeded in enrolling 26% of eligible patients. Whether this selection bias resulted in misleading interpretation could not be investigated, but, as mentioned, our methodological choices diminish the possible effects of such bias.

To further promote the 'ideal' nature of the trial, we only recruited experienced knee surgeons. Finally, to avoid possible problems concerning surgical trials with only one surgeon (Felson 2010), our trial included several surgeons. Is seems that the goal of enrolling those patients with the best anticipated outcome after APM was achieved, as the result of those declining (so-called 'open label', i.e., patients without any hesitation about the possibility of being assigned to sham surgery and thus having a 100% chance of experiencing the possible placebo effect) had in general better outcome than the cohort outside the RCT (Table 5).

11.3.2 Cohort

The cohort in this study included all patients undergoing arthroscopic partial meniscectomy due to non-traumatic (degenerative) meniscus tear at Hatanpää Hospital. One potential means to assess the external validity of this data is to compare the proportions of different knee arthroscopic procedures carried out at this institution

(2007 to 2011, n=1991) with those carried out throughout the whole of Finland (2011, n=25 795) (THL 2014). The percentage of meniscus resections and repairs of all knee arthroscopies was similar at Hatanpää Hospital and in Finland as a whole: 47.6% and 2.1% compared with 47.6% and 2.3% respectively. The respective mean ages of the patients undergoing these two operations was also similar: patients undergoing meniscus resection and repair at Hatanpää hospital were 51 and 32 years of age and 50 and 30 years in Finland overall. Also, the ratio for repair and resection was comparable between these two (in Hatanpää Hospital 4.4 repairs / 100 resections vs. 4.9 / 100 in Finland as a whole). Be it noted here, that the abovementioned numbers do not include that the numbers of procedures at Hatanpää Hospital in 2011 (257) are also included in those numbers for Finland as a whole in the same year. As the number is small, the effect on the evaluation can be estimated to be negligible.

Finally, according to most recent statistics from the USA, the percentage of meniscus resections (of all knee arthroscopies) is between 42% and 48% (Cullen, Hall et al. 2009; Kim, Bosque et al. 2011), and 70% of these patients were over 45 years of age (Cullen, Hall et al. 2009). In summary, it seems that our treatment algorithm and the characteristics of patients treated in Hatanpää Hospital is not only very comparable to that of Finland in general but also to that of the entire USA.

11.3.3   Definition of degenerative tear

One important question concerning the generalizability of the project lies in the definition of degenerative tear. The definition of the concepts 'degenerative' or 'traumatic' in the context of meniscus injuries is essentially arbitrary. Traditionally, meniscus injuries or tears have been classified as traumatic or degenerative according to morphology (tear pattern observed in MRI or at arthroscopy) or the aetiology (injury mechanism) but no validated and universally agreed criteria exist on making the distinction between the two entities (Larking 2010). Even the definition of the word 'trauma' is a challenge. Although a 'traumatic' onset of symptoms is indeed an exclusion criterion in this study, part of patients with a 'degenerative' meniscus tear do/did experience some kind of twisting movement or other relatively modest injury prior to the onset of their knee symptoms (Drosos and Pozo 2004; Camanho, Hernandez et al. 2006). In essence, our criteria for labelling a tear as 'traumatic' required a more significant event, such as falling from a chair, stairs or bicycle or slipping on ice or a sport-related injury. Our intention of excluding patients with clear

traumatic event did not mean that we would exclude all patients with sudden onset of symptoms, but rather only those younger patients with a meniscus tear in an otherwise healthy meniscus tissue associated with a clear knee trauma with haemarthron and ligamentous injury. Accordingly, all patients with sudden injuries related to their own voluntary muscle activities (such as kneeling, bending or kicking) and patients with a minor twisting of the knee were included in this study.

Although, in the most stringent sense, the results of this project are directly applicable only to patients with degenerative meniscus tears, based on the criteria mentioned above, we included most of the patients with a meniscal tear. Because of the RCT-within-a-cohort design, we are able to identify and assess this potential bias. During the recruitment period of the FIDELITY trial (from October 2007 to January 2012), there were another 587 patients aged 35 to 65 years with isolated meniscus tear requiring APM. Of these, only 28/587 (4%) were deemed to have had a truly traumatic onset of symptoms according to our eligibility criteria and they were thus excluded from the analysis. Our data on the incidence of traumatic tears is in agreement (or even more stringent) with that reported in earlier studies showing that most meniscus tears undergoing surgery are non-traumatic or degenerative in nature (Poehling, Ruch et al. 1990; Englund, Roos et al. 2001; Drosos and Pozo 2004; Metcalf and Barrett 2004; Christoforakis, Pradhan et al. 2005; Camanho, Hernandez et al. 2006) Further, the results of a post hoc subgroup analysis in the FIDELITY RCT limited to patients with a sudden onset of symptoms showed no significant benefit from arthroscopic partial meniscectomy over sham surgery. This is in perfect agreement with a recent study, which reported the outcome after the resection of degenerative meniscus tear being similar for those with distinct previous traumatic events and those without such an injury (Kim, Kim et al. 2013). Similarly, Camanho et al. found comparable results after APM among those with sudden onset of (fatigue) degenerative tear and those with progression of a degenerative process (Camanho, Hernandez et al. 2006). Based on this, our sample (and our results/interpretations) covers the majority of all meniscus tears. Finally, even after a traumatic meniscal tear, non- surgical treatment may result in full recovery or major improvement within a twelve-month follow-up period (Wagemakers, Luijsterburg et al. 2010).

11.4   Weaknesses of the study

11.4.1   Symptoms attributed to meniscus tear?

The diagnosis of meniscus tear has traditionally been based on the following clinical and radiological findings: patient's history (traumatic event), knee pain and other symptoms, especially catching and locking, pain provoked by palpation or compression of the joint line, special clinical meniscus tests, MRI imaging, and ultimately, arthroscopic examination (Solomon, Simel et al. 2001; Greis, Bardana et al. 2002). True traumatic tears (in younger individuals) virtually always occur due to a twisting injury or a hyperflexion event and they typically present with acute pain, swelling and even a locked knee (Greis, Bardana et al. 2002). In contrast, the diagnosis of degenerative meniscus tear poses a formidable challenge. Pain is generally considered the most important symptom of meniscus tear (Noble 1975; Rand 1985; Lim, Bae et al. 2010), but numerous reports show that meniscus tear is seldom the cause of knee pain and moreover, a large proportion of tears found in MRI (70-80 %) are asymptomatic. This is especially true for patients with knee OA (Bhattacharyya, Gale et al. 2003; Englund, Niu et al. 2007). Meniscus tears are frequently found in MRI also among asymptomatic patients even with no knee OA (Guermazi, Niu et al. 2012). Among patients with knee symptoms, the relevance of a meniscus tear has not been properly addressed. The same concerns apply to the clinical meniscus tests in patients with established knee OA, as it seems impossible to detect a meniscus tear by clinical examination (Dervin, Stiell et al. 2001). In patients with no knee OA, the only evidence of the ability of clinical meniscus tests to detect a tear comes from studies concerning mostly traumatic tears (Scholten, Deville et al. 2001; Solomon, Simel et al. 2001). However, increasing evidence suggests that degenerative meniscus tear may be an early sign of knee OA rather than a separate clinical entity in its own right (Bhattacharyya, Gale et al. 2003; Ding, Martel-Pelletier et al. 2007; Englund, Guermazi et al. 2008; Englund, Guermazi et al. 2009). For example, no significant association was found between the presence of meniscal damage and the development of frequent knee pain in middle-aged and older adults (Englund, Niu et al. 2007). This could be the explanation of our results (that APM is not efficient treatment). On the other side, because also the patients in the sham group got better soon after the intervention, there probably are also other factors regarding the source of knee pain and patients´ improvement.

12 SUMMARY AND CONCLUSIONS

This study showed that WOMET has acceptable psychometric properties and can therefore be used as a validated outcome measure for patients with degenerative knee disease. APM was found to be no better than sham surgery in the treatment of degenerative meniscus tear. So-called mechanical symptoms were found to be associated with poor knee status before and after arthroscopic surgery, as shown by the patients´ satisfaction and validated outcome measures. Also, the outcome after APM was not superior to that after sham surgery after stratification based on the existence of preoperative mechanical symptoms. Similarly, no difference was observed in the frequency of the occurrence of mechanical symptoms after surgery between the meniscectomy and sham surgery groups.

Only one randomized, sham-controlled trial of arthroscopic treatment for degenerative knee disease has so far been presented (Moseley, O'Malley et al. 2002). In patients with established knee osteoarthritis, arthroscopic lavage or debridement did not result in better outcomes than a sham procedure (skin incisions only). In a subsequent trial assessing the issue (a study that did not involve a sham-control), arthroscopic surgery coupled with optimized physical and medical therapy showed no significant benefit over optimized physical and medical therapy alone (Kirkley, Birmingham et al. 2008). In earlier trials assessing the benefit of arthroscopic partial meniscectomy in the treatment of a degenerative meniscal tear in patients with varying degrees of knee osteoarthritis, arthroscopic surgery and exercise therapy was not superior to exercise therapy alone (Herrlin, Wange et al. 2013; Katz, Brophy et al. 2013).

In a controlled (not blinded) trial of surgery versus conservative treatment, it is only possible to study if surgery (or conservative treatment) works better. If the outcome after surgery is better, the interpretation of the results is somewhat challenging, as there is really no way to conclude whether the surgery itself or the placebo effect associated with surgery is attributable for the observed intervention-induced improvement. If no difference exists, one could naturally conclude that surgery does not seem to provide a benefit over conservative treatment. Sham/placebo controlled

trial is the only way to assess the true efficacy of surgical intervention. Why is this important? One of the most understandable ways to communicate this was offered by Archie Cochrane, when he introduced his hierarchy of evidence: To show that any intervention in medicine is worthwhile, it should pass the following scrutiny: First, one has to study the effect of the treatment under idealized conditions (can it work?), then under normal conditions (the effectiveness: does it work?) and if both are proven, finally show that this intervention is cost-effective (is it worth it?). All those steps should be investigated first, and not until all are found to be positive, should the treatment be adopted in ordinary practise (Haynes 1999; Jarvinen, Sievanen et al. 2011).

All these earlier trials (in addition to that by Moseley) assessed whether arthroscopic surgery confers a benefit in ordinary health care settings (i.e. they were effectiveness trials involving patients with typical degenerative knee disease and varying degrees of knee osteoarthritis). In contrast, our FIDELITY trial assessed whether arthroscopic partial meniscectomy is effective under "ideal" circumstances. Accordingly, we selected patients who would be expected to benefit from arthroscopic partial meniscectomy — those with a degenerative tear of the medial meniscus and no osteoarthritis. The use of a sham-surgery control, with study-group assignments concealed from patients as well as from those collecting data and analysing the outcomes further increased the rigour of our trial. The results and the inferences of the present study are in perfect agreement with those of earlier studies; APM is not effective treatment for patients with degenerative meniscus tear.

In general, this study demonstrated that the current indications for knee arthroscopy of patients with a degenerative knee disease (degenerative meniscus tear with or without mechanical symptoms) should be questioned. The study should lead to a change in practice among orthopaedic surgeons, and in the recommendations by the orthopaedic associations, as well as in the reimbursement policies of health care authorities and insurance companies. Re-prioritisation of the indications for elective orthopaedic surgery is proposed.

13 FUTURE DIRECTIONS

Further studies are needed to investigate whether physical therapy or watchful waiting or doing nothing is the best way to treat patients with knee pain and early OA/degenerative meniscus tear. Also the optimal exercise programme needs to be determined, including characterization by type and intensity of exercise, length of the programme, duration of individual sessions, and number of sessions per week and finally, if it should be supervised or not.

In this study patients with traumatic meniscus tear were excluded. Although our post hoc analysis showed no difference in outcome between those with sudden onset of symptoms and those with gradual onset of symptoms, the efficacy of APM should be studied in this population. As there is no high quality study to assess the efficacy of APM nor meniscus repair after traumatic incidence, further high quality studies are warranted to determine the role of meniscus repair/restoration, resection or non-surgical management after traumatic meniscus tears.

The question of the pathomechanism of knee OA should be studied further; there are two distinct theories, namely mechanical (Felson 2013) and inflammatory (Berenbaum 2013) for which the association of meniscus tear with OA should also be explored. There are probably two totally different kinds of knee OA associated with meniscus tears. First, the mechanical one, which is brought about by the trauma itself and resection of traumatic tear leading to a decreased knee function and possible malalignement of the knee, for which there is evidence of an association with knee OA. Especially the role of traumatic injury for chondral surfaces and for initiation of OA should be investigated. Second, there is an inflammatory/biological/degenerative form of knee OA where female gender and obesity constitute main risk factors, which includes degeneration of the menisci and chondral surfaces. Further studies are warranted on the association of degenerative meniscus tear and knee OA to assess the prognostic effect of a meniscus tear *per se* and degenerative process in general for increased risk of knee OA.

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16   ORIGINAL COMMUNICATIONS