**Knee Arthroscopy Cohort Southern Denmark (KACS): Protocol for a prospective cohort study**

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Knee Arthroscopy Cohort Southern Denmark (KACS):

Protocol for a prospective cohort study

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ABSTRACT

Background

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States. The procedure is considered trivial since patients leave the hospital a few hours after surgery. Little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and factors affecting these outcomes. A critical oversight of previous studies is their failure to account for the type of meniscal tear. Meniscus tears can be categorized as traumatic or non-traumatic. Traumatic tears are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint. Non-traumatic tears (i.e. degenerative tears) are typically observed in the middle-aged (35-55 years) and older population but the etiology is unclear. It is not known if the effect of arthroscopic meniscus surgery on patient symptoms differs between patients with traumatic and non-traumatic tears. The aim of this prospective cohort study is to investigate the natural time course of patient-reported outcomes in patients undergoing meniscus surgery, with particular emphasis on the role of the type of meniscus tear.

Methods/Design

This prospective cohort study enrol patients assigned for meniscus surgery. At baseline (PRE surgery), patient characteristics are assessed using an email-based questionnaire also comprising several validated questionnaires assessing general health, knee-specific characteristics and patient’s expectations of the surgery. Follow-up will be conducted at 12 and 52 weeks after meniscus surgery. The major outcomes will be differences in changes, from before to 52 weeks after surgery, in each of the 5 domains on the Knee Injury and Osteoarthritis Outcome Score (KOOS) between
patients undergoing surgery for traumatic compared with non-traumatic meniscus tears.

Dissemination

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

Trial registration number: ClinicalTrials.gov Identifier: NCT01871272

Key words: Cohort Study, Arthroscopy, Knee, Prospective Studies, Meniscus

Article focus

- This article describes a study protocol for a prospective cohort study investigating the natural time course of patient reported outcomes after arthroscopic meniscus surgery.

Key messages

- The study will have particular emphasis on the importance of type of meniscus tear (i.e. traumatic or non-traumatic), which may have important implications for improvements in patients reported outcomes after surgery.

Strengths and limitations of this study

- This cohort study will provide information on the natural time course of patient reported outcomes in a large group of patients after arthroscopic meniscus surgery. Patients with reconstruction of the anterior or posterior cruciate ligament will not be included in the KACS cohort.
INTRODUCTION

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States [1] at an average cost of $5,000/procedure [2]. The procedure is often considered trivial since patients leave the hospital few hours after surgery. Nevertheless, little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and which factors affect these outcomes [3]. One explanation may be that the loss of meniscal function triggers other events that may cause knee pain [4]. Further, the “placebo effect” of arthroscopic surgery needs to be taken into account [2]. The general opinion is that patients recover their muscle strength fully within 6-12 weeks following arthroscopic partial meniscectomy [5-7]. Importantly, however, recent studies have shown substantial patient-reported disability and pain in patients up to 4 years after surgery [8-10]. A critical limitation of previous studies is their failure to account for the type of meniscal tear.

Meniscus tears can be categorized as either traumatic or non-traumatic. Traumatic tears (TT) are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint, and can be attributed to a specific incident (e.g. sports related trauma) [11]. TT’s are often associated with joint effusion, reduced knee joint range of motion (ROM) together with catching/locking of the knee. These ‘mechanical’ problems may be resolved with meniscus surgery (i.e. repair or resection). Non-traumatic tears (NTT) are typically observed in the middle-aged (35-55 years) and older population [12]. Risk factors for these tears include; presence of Heberdén’s and Bouchard nodes and knee malalignment [13], however the etiology is largely unclear [11]. NTT’s are often referred to as degenerative tears and are
suggested to be associated with incipient knee osteoarthritis (OA) in the middle-aged or elderly population [14-16]. Evidence from four well-designed trials demonstrated that arthroscopic interventions [2, 17] and meniscectomy [18-20] were no better, or provided no additional effect, than the comparator (i.e. sham surgery, physical therapy or a combination of physical and medical therapy) to relieve pain and improve function in middle-aged patients with knee OA or early signs of knee OA. No corresponding randomized trials exist specifically for TT but an observational study showed that patients with degenerative meniscus lesions (i.e. NTT) self-report worse function and quality of life compared to individuals with traumatic tears at follow-up 14 years after meniscectomy [21]. Thus, it is conceivable, but currently unproven, that arthroscopic meniscus surgery is more effective in resolving symptoms of a meniscus tear of traumatic aetiology compared with non-traumatic tears in the middle-aged population.

In patients with TT, repair of the meniscus may be an alternative to resection. Repair is rarely an option for middle-aged patients with NTT due to the degenerative state of the meniscus. A recent retrospective observational study suggested a reduced risk of later knee OA and less activity level loss in patients (~32 years at time of surgery) undergoing repair compared to resection (i.e. favoring repair) [22]. This indicates that patients with TT should be stratified into sub-groups on the basis of type of arthroscopic intervention (i.e. repair (TT\textsubscript{REP}) and resection (TT\textsubscript{RES})) since this may influence patient perceived outcomes after surgery.

Aims and hypotheses

The primary aims of this observational cohort are to:
(1) Investigate if improvements in patient self-reported pain, symptoms, function and quality of life differ after arthroscopic meniscus surgery for non-traumatic meniscus tears in middle-aged patients, compared with surgery in patients with traumatic tears (i.e., NTT vs. TT). We hypothesize that in middle-aged patients with NTT arthroscopic surgery is less effective in relieving self-reported pain, symptoms, function in sports and recreation and quality of life (i.e. change in KOOS scores), compared to younger patients undergoing surgery for TT.

(2) Investigate the effect of meniscus repair (TT\textsubscript{REP}) compared to meniscus resection (TT\textsubscript{RES}) on change in self-reported pain, symptoms, function in sports and recreation and quality of life in patients with TT. We hypothesize that arthroscopic surgery is less effective in relieving pain, symptoms, function in sports and recreation and quality of life (i.e., change in KOOS scores) in patients undergoing TT\textsubscript{RES} compared to those undergoing TT\textsubscript{REP}.

**METHODS AND ANALYSIS**

**Design**

In this prospective cohort study we will assess patient-reported outcomes (PROs) using email-based questionnaires prior to surgery and at 12 and 52 weeks follow-up post surgery (see Figure 1).

*(Insert Figure 1 around here)*

**Participants**
All patients assigned for arthroscopy on suspicion of a meniscus tear at Lillebælt Hospital (located in the cities Vejle and Kolding, Denmark) and Odense University Hospital, Denmark (incl. Svendborg Hospital) from February 1st 2013 to January 31st 2014.

General cohort eligibility criteria:

Inclusion criteria: Patients ≥18 years of age assigned for arthroscopy on suspicion of a medial and/or lateral meniscus tear, having an email address and able to read and understand Danish.

Exclusion criteria: Patients who will or previously have undergone surgical reconstruction of the anterior or posterior cruciate ligament (ACL or PCL) in either knee, suffered fracture(s) to the lower extremities (i.e. hip, leg or foot) in either leg within the last 6 months at time of recruitment and patients not mentally able to reply the questionnaire. Please refer to Figure 2 for an overview of the recruitment flow.

Wide inclusion criteria are set to allow for later sub-group analysis. Patients with reconstructed ACL and PCL cannot be included as these patients are being followed in another cohort study.

Inclusion and exclusion criteria, aim 1 (NTT vs. TT):

There is no consensus on how to classify patients as having a NTT or TT. In this study, patients undergoing meniscus surgery will be classified as having either TT or
NTT according to an algorithm based on age, duration of knee symptoms and one question about injury mechanism (see below). This represents the information that is available prior to surgery.

Injury mechanism question:

“How did the knee pain/problems for which you are now having surgery develop (choose the answer that best match your situation)?”

Response alternatives:

a. The pain/problems have slowly evolved over time
b. As a result of a specific incident (i.e. kneeling, sliding, twisting of the knee or the like)
c. As a result of a violent incident (i.e. during sports, a crash, collision or the like)

TT:
Inclusion: All patients between 18-34 years and all patients between 35-55 years replying “c” on the injury mechanism question.

NTT:
Inclusion: All patients between 35-55 years replying “a” or “b” on the injury mechanism question and having knee symptoms >6 months.

In addition, the general eligibility criteria also apply. For aim 1, the upper age limit is set to include patients with degenerative meniscus tears (i.e. NTT) but without severe features of knee OA [23].
Inclusion and exclusion criteria, aim 2 (TT\textsubscript{RES} vs. TT\textsubscript{REP}):  

All patients classified as TT according to the specific KACS eligibility criteria for aim 1 will be further divided in patients having either meniscus resection (TT\textsubscript{RES}) or repair (TT\textsubscript{REP}) according to the type of surgery they receive to answer study aim 2.

Patient characteristics

At baseline, self-report information about: Educational level, employment, civil status, smoking habits, co-morbidities [24], physical activity level [25] and self-reported knee and foot alignment [26] will be collected together with information on height and weight. Surgery documentation will be collected using a modified version of the ISAKOS Classification of Meniscal Tears questionnaire [27], which is filled out by the operating surgeon. Additional surgery information not pertaining to the meniscus is also collected from surgery reports.

Major Outcomes

Knee Injury and Osteoarthritis Outcome Score (KOOS)

All 5 domains (i.e., subscales) on the KOOS [28, 29] at the 1-year follow-up. The 5 KOOS domains are; pain, symptoms, function during daily activities (ADL), sport and recreational function (Sport/Rec) and quality of life (QOL). The KOOS score is ranging from 0-100 (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS score has been validated and previously used to assess self-
reported outcomes in patients undergoing meniscus surgery [8, 10, 18, 20, 28, 29].

All outcomes included in the study are listed in Table 1.

Minor Outcomes

Patient Acceptable Symptom State (PASS) and treatment failure (TF)

One question regarding PASS will be used to assess how many patients consider themselves well after surgery (as opposed to feeling better) [30]. PASS is assessed as a dichotomous outcome (y/n) to the question: “Considering your knee function, do you feel that your current state is satisfactory? With knee function you should take into account all activities you have during your daily life, sport and recreational activities, your level of pain and other symptoms, and also your knee related quality of life”.

In addition, patients replying “no” to the PASS question will also be asked to answer (y/n) the following question: “Would you consider your current state as being so unsatisfactory that you think the treatment has failed?”. Patients replying, “yes” to the second question will be defined as experiencing “treatment failure” (TF).

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The SF-36 will be used to assess general physical function. The SF-36 consists of 8 subscales: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The SF-36 is self-explanatory, takes 10 minutes to complete, and is scored from 0–100 (0 indicating extreme problems and 100 indicating no problems). The Acute Danish version of the SF-36 was used [31, 32].

Table 1: Collection of patient characteristics, outcome measures and explanatory
variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRE</th>
<th>Surgery</th>
<th>12weeks</th>
<th>52 weeks</th>
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<td>Knee joint stability</td>
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ISAKOS = International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) Classification of Meniscal Tears questionnaire; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; KOOS = Knee Injury and Osteoarthritis Outcome Score; PASS = Patient Acceptable Symptom State; TF = Treatment Failure; GPE = Global Perceived Effect; AE = Adverse Events.
Exploratory Outcomes

- Questions regarding patient expectations of surgery [33].
- Questions concerning knee joint stability/laxity. One question regarding frequency of symptoms and one question about the influence of symptoms (i.e. sense of instability during daily activities).
- Questions regarding postoperative rehabilitation (i.e. participation, type, frequency and degree of supervision).
- Questions regarding global perceived effect (GPE) to explore minimal clinical important change in patient-reported outcomes. GPE is evaluated on a seven-step global rating scale after surgery (ranging from better, an important improvement; somewhat better, but enough to be an important improvement; very small change, not enough to be an important improvement; about the same; very small change, not enough to be an important worsening; somewhat worse, but enough to be an important worsening; worse, an important worsening). A two-step change in GPE is considered clinically important [34].

Adverse events (AE)

Adverse events (not necessarily implying causality to the surgery), defined as self-reported symptoms after surgery causing limitations in daily activities, sport and recreational activities or work limitations together with symptoms causing patients to seek medical care or having re-surgery will be collected by self-report and patient record review.

Data management
All self-reported data are collected using email-based questionnaires. Participant submitted responses are automatically registered in a secured database. At all data collection points an email reminder is sent to participants if they do not answer the email-based questionnaire within 3-4 days. In addition, participants who do not reply after the reminder will be called by phone to ensure a high follow-up rate.

Information registered by surgeons on the modified ISAKOS questionnaire following surgery will be transferred from paper format to electronic format using Automated Forms Processing. This method is a validated alternative to double entry of data [35].

Statistical analysis

The cohort will recruit all eligible patients from February 1st 2013 to January 31st 2014. Conservatively estimated we expect to recruit 450 patients to the KACS cohort within this timeframe. For an overview of the expected distribution of patients recruited between 18 and 55 years, please refer to Figure 3.

The minimal clinically important change (MCIC) on the KOOS subscale is considered to be 8-10 points [36]. Thus, with the estimated recruitment flow and distribution (Figure 3) we will have a power of 0.99 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean difference of 8 KOOS points between NTT and TT (primary study aim 1).

In addition, we will have a power of 0.88 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean difference of 10 KOOS points between TTRES and TTREP (study aim 2).
If we are not able to reach sufficient numbers within the one year timeframe, recruitment will continue until the numbers specified in the *a priori* sample size calculation are reached.

*(Insert Figure 3 around here)*

Descriptive results will be given as means with standard deviations (or medians with interquartile range) and as percentages. Between-group comparisons of the KOOS and SF-36 scores at the 52 weeks follow-up will be analyzed with the use of ANalysis of COVAriance (ANCOVA), stratified by site and adjusted for the preoperative score level, sex, age, and BMI. PASS and TF will be analysed using chi-square test. Multiple logistic regression will be applied to estimate odds ratios for dichotomous outcomes. Mixed linear effects models with patient as random factor and sex, age and BMI as fixed factors will be used to explore change over time (i.e. baseline, 12 weeks and 52 weeks follow-up) in KOOS and SF-36 scores. Results will be presented with 95% confidence intervals. No interim analysis will be performed. All reported P values are two-sided and will not be adjusted for multiple comparisons. All data analyses will be carried out according to the pre-established analysis plan. All descriptive statistics and tests will be reported in accordance to the recommendations of the ‘Enhancing the QUAlity and Transparency Of health Research’ (EQUATOR) network: the STROBE statement[37].

**Full analysis set**

To qualify for the “full analysis set” recruited patients must reply to the baseline questionnaire and have surgery performed to their meniscus. Please refer to Figure 4,
for an overview of the full analysis set. In case of missing data a non-responder
imputation will be applied (i.e. baseline observation carried forward). Further for
sensitivity, the effect that any missing data might have on results will be assessed via
sensitivity analyses of augmented data sets.

(Insert Figure 4 around here)

Planned sensitivity analysis

Sensitivity analysis will be conducted to explore whether the degree of cartilage
defects (score: 0-4), and plica presence (y/n) have any impact on the outcome after
surgery. Furthermore, we will construct a dichotomous outcome on whole knee OA
(y/n) to explore the effect of presence of knee OA. Whole knee OA will be defined as;
participants with cartilage defects ICRS grade >2 in either of the patellofemoral,
medial tibiofemoral or lateral tibiofemoral compartment excluding participants with
TT (according to previous definition) and symptoms <6 months. In addition, the
effect of differences in patient characteristics between groups reported in table 1 with
a p-value less or equal to 0.10 will be tested in a fully adjusted model.

ETHICS AND DISSEMINATION

The Regional Scientific Ethics Committee of Southern Denmark has reviewed the
outline of this cohort study. The committee waived the need for ethical approval as
the study is only pertaining questionnaire and register data. Such studies can be
implemented without permission from the Ethics Committee according to Danish
legislation (Committee Act § 1, paragraph 1).
The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

DISCUSSION

Arthroscopic meniscus surgery is high volume surgery[1]. Little is known about the natural time course of patient-reported outcomes after meniscus surgery and which factors affect these outcomes. This prospective cohort will collect data on the natural time course of patient-reported outcomes prior and following arthroscopic meniscus surgery. Our results will enable analysis of the dependence of post surgery outcome on type of meniscus tear (i.e. TT vs. NTT in middle-aged patients). Further, it will be possible to investigate the dependence of post surgery outcome on type of surgery in the sub-group of patients with traumatic tears (i.e. TT_{RES} vs. TT_{REP}).

In this study a pragmatic clinical approach was chosen to categorize meniscus tears as either TT or NTT (i.e. degenerative). The advantages of this approach are that it is simple, cheap, can be determined prior to surgery (in contrast to histology or arthroscopic observation), and feasible in a routine clinical setting. Thus, this information can be used to form an algorithm based on information available prior to surgery to select those patients who benefit most from surgery, which can be implemented in clinical practice.

A limitation to this study is that patients are included based on the main reason for surgery (i.e. suspicion of a meniscus tear). However, meniscus surgery may also be performed in relation to surgery for other knee pathologies. Those patients will not be included in the Knee Arthroscopy Cohort of Southern Denmark (KACS). This
should be taken into account when interpreting the cohort data. On the other hand this makes it more likely that patient symptoms in the KACS cohort are primarily caused by the meniscus injury.

Meniscus surgery may not be the answer to improve patient perceived pain and function in all patients with meniscus tears. Different factors, such as type of tear, may affect the post-operative outcome. Ultimately the goal of this study is to improve management of patients with meniscus tears through identifying factors associated with no or limited effect of surgery on patient-reported outcomes.

CONTRIBUTIONS

JBT and LSL conceived the study. All authors participated in the study design. JBT, RC and LSL drafted the manuscript. All authors participated in critical scrutinizing and revision of the manuscript and approved the final version.

FUNDING

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COMPETING INTERESTS

None
REFERENCES


Figure 1: Overview of collection of outcomes during the first year in the KACS cohort.
Figure 2: Overview of the recruitment flow in the KACS cohort.

Recruitment flow

All patients conforming with inclusion criteria are invited to participate in the study when assigned for meniscus surgery

Excluded:
- Self-reported ACL or PCL reconstruction to either knee
- Self-reported fractures to the lower extremities within previous 6 months

Baseline assessment of eligible patients accepting invitation to participate

Surgery

Excluded:
- Patients with no meniscus injury at surgery

Patients eligible for 12 weeks follow-up assessment

Patients eligible for 52 weeks follow-up assessment
Figure 3: Expected distribution per 450 patients recruited, divided by age, type of tear and type of surgery.

NTT = non-traumatic tear, TT = traumatic tear, TT_{RES} = traumatic tear resected, TT_{REP} = traumatic tear repaired.
Figure 4: Overview of the full analysis set for study aim 1 and 2. NTT = non-traumatic tear, TT = traumatic tear, TTRES = traumatic tear resected, TTREP = traumatic tear repaired.
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ABSTRACT

Background

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States. The procedure is conducted on an outpatient basis and patients leave the hospital few hours after surgery. A critical oversight of previous studies is their failure to account for the type of meniscal tear. Meniscus tears can be categorized as traumatic or non-traumatic. Traumatic tears are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint. Non-traumatic tears (i.e. degenerative tears) are typically observed in the middle-aged (35-55 years) and older population but the etiology is largely unclear. Knowledge about the potential difference of the effect of arthroscopic meniscus surgery on patient symptoms between patients with traumatic and non-traumatic tears is sparse. Furthermore, little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and factors affecting these outcomes. The aim of this prospective cohort study is to investigate the natural time course of patient-reported outcomes in patients undergoing meniscus surgery, with particular emphasis on the role of type of symptom onset.

Methods/Design

This prospective cohort study enrol patients assigned for meniscus surgery. At baseline (PRE surgery), patient characteristics are assessed using an email-based questionnaire also comprising several validated questionnaires assessing general health, knee-specific characteristics and patient’s expectations of the surgery. Follow-up will be conducted at 12 and 52 weeks after meniscus surgery. The major outcomes will be differences in changes, from before to 52 weeks after surgery, in each of the 5 domains on the Knee Injury and Osteoarthritis Outcome Score (KOOS) between
patients undergoing surgery for traumatic compared with non-traumatic meniscus tears.

Dissemination

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

Trial registration number: ClinicalTrials.gov Identifier: NCT01871272

Key words: Cohort Study, Arthroscopy, Knee, Prospective Studies, Meniscus

Article focus

- This article describes a study protocol for a prospective cohort study investigating the natural time course of patient reported outcomes after arthroscopic meniscus surgery.

Key messages

- This study will provide information about the natural time course and potential difference in improvement in patient reported outcomes after arthroscopic meniscus surgery for traumatic and non-traumatic tears.

Strengths and limitations of this study

- This cohort study collects data on the natural time course of patient reported outcomes in a clinical setting on a large group of patients after arthroscopic meniscus surgery to ensure high external validity.

- As data is collected on a large number of patients in a clinical setting it was not feasible to collect standardized imaging data (i.e. MRI or radiographs) on patients, which could have provided valuable information.
INTRODUCTION

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States [1]. The procedure is conducted on an outpatient basis and patients leave the hospital few hours after surgery. Nevertheless, little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and which factors affect these outcomes [2]. The general opinion is that patients recover their muscle strength fully within 6-12 weeks following arthroscopic partial meniscectomy [3-5]. Importantly, however, recent studies have shown substantial patient-reported disability and pain in patients up to 4 years after surgery [6-8]. One explanation for the poor self-reported outcomes may be that the loss of meniscal function triggers other events that may cause knee pain [9]. Complicating the assessment of surgery effectiveness further, surgical procedures have shown to be associated with considerable “placebo effect” [10, 11].

A critical limitation of previous studies [12-15] is their failure to account for the type of symptom onset (i.e. injury mechanism). Meniscus tears can be categorized as either traumatic or non-traumatic. Traumatic tears (TT) are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint, and can be attributed to a specific incident (e.g. sports related trauma) [16]. TT’s are often associated with joint effusion, reduced knee joint range of motion (ROM) together with catching/locking of the knee. Non-traumatic tears (NTT) are typically observed in the middle-aged (35-55 years) and older population [17]. These tears are associated with meniscal calcification [18] and risk factors for these tears include; presence of Heberdén’s and Bouchard nodes, knee malalignment [19] and occupational kneeling [20], however the etiology is largely unclear [16]. NTT’s are often referred to as
degenerative tears and have been shown to be associated with incipient knee osteoarthritis (OA) in the middle-aged or elderly population [21-23]. Evidence from four well-designed trials demonstrated that arthroscopic interventions [10, 24] and meniscectomy [25-27] were no better, or provided no additional effect, than the comparator (i.e. sham surgery, physical therapy or a combination of physical and medical therapy) to relieve pain and improve function in middle-aged patients with knee OA or early signs of knee OA. No corresponding randomized trials exist specifically for TT but an observational study showed that patients with degenerative meniscus lesions (i.e. NTT) self-report worse function and quality of life compared to individuals with traumatic tears at follow-up 14 years after meniscectomy [28]. Thus, it is conceivable, but currently unproven, that arthroscopic meniscus surgery is more effective in resolving symptoms of a meniscus tear of traumatic aetiology compared with non-traumatic tears in the middle-aged population.

In patients with TT, repair of the meniscus may be an alternative to resection. In contrast, repair is rarely an option for middle-aged patients with NTT due to the degenerative state of the meniscus. A recent retrospective observational study suggested a reduced risk of later knee OA and less activity level loss in patients (~32 years at time of surgery) undergoing repair compared to resection (i.e. favoring repair) [29]. This indicates that patients with TT should be stratified into sub-groups on the basis of type of arthroscopic intervention (i.e. repair (TT<sub>REP</sub>) and resection (TT<sub>RES</sub>)) since this may influence patient perceived outcomes after surgery.

Aims and hypotheses

The primary aims of this observational cohort are to:
(1) Investigate if improvements in patient self-reported pain, symptoms, function and quality of life differ after arthroscopic meniscus surgery for non-traumatic meniscus tears in middle-aged patients, compared with surgery in patients with traumatic tears (i.e., NTT vs. TT). We hypothesize that in middle-aged patients with NTT arthroscopic surgery is less effective in relieving self-reported pain, symptoms, function in sports and recreation and quality of life (i.e. change in KOOS scores), compared to younger patients undergoing surgery for TT.

(2) Investigate the effect of meniscus repair (TTREP) compared to meniscus resection (TTRES) on change in self-reported pain, symptoms, function in sports and recreation and quality of life in patients with TT. We hypothesize that arthroscopic surgery is less effective in relieving pain, symptoms, function in sports and recreation and quality of life (i.e., change in KOOS scores) in patients undergoing TTRES compared to those undergoing TTREP.

METHODS AND ANALYSIS

Design

In this prospective cohort study we will assess patient-reported outcomes (PROs) using email-based questionnaires prior to surgery and at 12 and 52 weeks follow-up post surgery (see Figure 1).

(Insert Figure 1 around here)

Participants
All patients assigned for arthroscopy on suspicion of a meniscus tear at Lillebælt Hospital (located in the cities Vejle and Kolding, Denmark) and Odense University Hospital, Denmark (incl. Svendborg Hospital) from February 1st 2013 to January 31st 2014.

General cohort eligibility criteria:

Inclusion criteria: Patients ≥18 years of age assigned for arthroscopy on suspicious of a medial and/or lateral meniscus tear by the examining orthopaedic surgeon based on clinical signs and MRI (if available), having an email address and able to read and understand Danish.

Exclusion criteria: Patients who will or previously have undergone surgical reconstruction of the anterior or posterior cruciate ligament (ACL or PCL) in either knee, suffered fracture(s) to the lower extremities (i.e. hip, leg or foot) in either leg within the last 6 months at time of recruitment and patients not mentally able to reply the questionnaire. Please refer to Figure 2 for an overview of the recruitment flow.

(Insert Figure 2 around here)

Patients with reconstructed ACL and PCL cannot be included as these patients are being followed in another cohort study.

Inclusion and exclusion criteria, aim 1 (NTT vs. TT):

There is no consensus on how to classify patients as having a NTT or TT. In this study, patients undergoing meniscus surgery will be classified as having either TT or
NTT according to an algorithm based on age, duration of knee symptoms and one question about injury mechanism (see below). This represents the information that is available prior to surgery.

Injury mechanism question:

“How did the knee pain/problems for which you are now having surgery develop (choose the answer that best match your situation)?”

Response alternatives:

a. The pain/problems have slowly evolved over time
b. As a result of a specific incident (i.e. kneeling, sliding, twisting of the knee or the like)
c. As a result of a violent incident (i.e. during sports, a crash, collision or the like)

TT:

Inclusion: All patients between 18-34 years and all patients between 35-55 years replying “c” on the injury mechanism question.

NTT:

Inclusion: All patients between 35-55 years replying “a” or “b” on the injury mechanism question and having knee symptoms >6 months.

In addition, the general eligibility criteria also apply. For aim 1, the upper age limit is set to include patients with degenerative meniscus tears (i.e. NTT) but without severe
features of knee OA [30]. Furthermore, patients which responses do not fit the TT and NTT criteria will also be excluded.

Inclusion and exclusion criteria, aim 2 (TT\textsubscript{RES} vs. TT\textsubscript{REP}):

All patients classified as TT according to the specific KACS eligibility criteria for aim 1 will be further divided in patients having either meniscus resection (TT\textsubscript{RES}) or repair (TT\textsubscript{REP}) according to the type of surgery they receive to answer study aim 2.

Patient characteristics

At baseline, self-report information about: Educational level, employment, civil status, smoking habits, co-morbidities [31], physical activity level [32] and self-reported knee and foot alignment [33] will be collected together with information on height and weight. Surgery documentation will be collected using a modified version of the ISAKOS Classification of Meniscal Tears questionnaire[34], which is filled out by the operating surgeon. Additional surgery information not pertaining to the meniscus is also collected from surgery reports.

Major Outcomes

Knee Injury and Osteoarthritis Outcome Score (KOOS)

All 5 domains (i.e., subscales) on the KOOS [35, 36] at the 1-year follow-up. The 5 KOOS domains are; pain, symptoms, function during daily activities (ADL), sport and recreational function (Sport/Rec) and quality of life (QOL). The KOOS score is ranging from 0-100 (0 indicating extreme symptoms and 100 indicating no
symptoms). The KOOS score has been validated and previously used to assess self-reported outcomes in patients undergoing meniscus surgery [6, 8, 25, 27, 35, 36]. In addition, it has been shown to perform well in the entire continuum from very early changes of knee OA to knee arthroplasty [37]. All outcomes included in the study are listed in Table 1.

Minor Outcomes

Patient Acceptable Symptom State (PASS) and treatment failure (TF)

One question regarding PASS will be used to assess how many patients consider themselves well after surgery (as opposed to feeling better) [38]. PASS is assessed as a dichotomous outcome (y/n) to the question: “Considering your knee function, do you feel that your current state is satisfactory? With knee function you should take into account all activities you have during your daily life, sport and recreational activities, your level of pain and other symptoms, and also your knee related quality of life”.

In addition, patients replying “no” to the PASS question will also be asked to answer (y/n) the following question: “Would you consider your current state as being so unsatisfactory that you think the treatment has failed?”. Patients replying, “yes” to the second question will be defined as experiencing “treatment failure” (TF).

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The SF-36 will be used to assess general physical function. The SF-36 consists of 8 subscales: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The SF-36 is self-explanatory, takes 10 minutes to complete, and is scored from 0–100 (0 indicating extreme problems and
100 indicating no problems). The Acute Danish version of the SF-36 was used [39, 40].

Table 1: Collection of patient characteristics, outcome measures and explanatory variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRE</th>
<th>Surgery</th>
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<th>52 weeks</th>
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<td>Weight</td>
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<td>Smoking</td>
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<td>Co-morbidities</td>
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<tr>
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<tr>
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<tr>
<td>Knee joint stability</td>
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<td>Expectations for surgery</td>
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<td>KOOS</td>
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<tr>
<td>AE</td>
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</table>

ISAKOS = International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) Classification of Meniscal Tears questionnaire; SF-36 = Medical Outcomes Study 36-Item
Short Form Health Survey; KOOS = Knee Injury and Osteoarthritis Outcome Score; PASS = Patient Acceptable Symptom State; TF = Treatment Failure; GPE = Global Perceived Effect; AE = Adverse Events

Exploratory Outcomes

- Questions regarding patient expectations of surgery [41].
- Questions concerning knee joint stability/laxity. One question regarding frequency of symptoms and one question about the influence of symptoms (i.e. sense of instability during daily activities).
- Questions regarding postoperative rehabilitation (i.e. participation, type, frequency and degree of supervision).
- Questions regarding global perceived effect (GPE) to explore minimal clinical important change in patient-reported outcomes. GPE is evaluated on a seven-step global rating scale after surgery (ranging from better, an important improvement; somewhat better, but enough to be an important improvement; very small change, not enough to be an important improvement; about the same; very small change, not enough to be an important worsening; somewhat worse, but enough to be an important worsening; worse, an important worsening). A two-step change in GPE is considered clinically important [42].

Adverse events (AE)

Adverse events (not necessarily implying causality to the surgery), defined as self-reported symptoms after surgery causing limitations in daily activities, sport and recreational activities or work limitations together with symptoms causing patients to
seek medical care or having re-surgery will be collected by self-report and patient record review.

Data management

All self-reported data are collected using email-based questionnaires. Participant submitted responses are automatically registered in a secured database. At all data collection points an email reminder is sent to participants if they do not answer the email-based questionnaire within 3-4 days. In addition, participants who do not reply after the reminder will be called by phone to ensure a high follow-up rate.

Information registered by surgeons on the modified ISAKOS questionnaire following surgery will be transferred from paper format to electronic format using Automated Forms Processing. This method is a validated alternative to double entry of data [43].

Statistical analysis

The cohort will recruit all eligible patients from February 1st 2013 to January 31st 2014. Conservatively estimated we expect to recruit 450 patients to the KACS cohort within this timeframe. For an overview of the expected distribution of patients recruited between 18 and 55 years, please refer to Figure 3.

The minimal clinically important change (MCIC) on the KOOS subscale is considered to be 8-10 points [37]. Thus, with the estimated recruitment flow and distribution (Figure 3) we will have a power of 0.99 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean
difference of 8 KOOS points between NTT and TT (primary study aim 1).

In addition, we will have a power of 0.88 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean difference of 10 KOOS points between TT\textsubscript{RES} and TT\textsubscript{REP} (study aim 2).

If we are not able to reach sufficient numbers within the one year timeframe, recruitment will continue until the numbers specified in the \textit{a priori} sample size calculation are reached.

\textit{(Insert Figure 3 around here)}

Descriptive results will be given as means with standard deviations (or medians with interquartile range) and as percentages. Between-group comparisons of the KOOS and SF-36 scores at the 52 weeks follow-up will be analyzed with the use of ANalysis of COVAriance (ANCOVA), stratified by site and adjusted for the preoperative score level, sex, age, and BMI. PASS and TF will be analysed using chi-square test. Multiple logistic regression will be applied to estimate odds ratios for dichotomous outcomes. Mixed linear effects models with patient as random factor and sex, age and BMI as fixed factors will be used to explore change over time (i.e. baseline, 12 weeks and 52 weeks follow-up) in KOOS and SF-36 scores. Results will be presented with 95% confidence intervals. No interim analysis will be performed. All reported P values are two-sided and will not be adjusted for multiple comparisons. All data analyses will be carried out according to the pre-established analysis plan. All descriptive statistics and tests will be reported in accordance to the recommendations of the ‘Enhancing the QUAlity and Transparency Of health Research’ (EQUATOR)
network: the STROBE statement[44].

Full analysis set

To qualify for the “full analysis set” recruited patients must reply to the baseline questionnaire and have surgery performed to their meniscus. Please refer to Figure 4, for an overview of the full analysis set. In case of missing data a non-responder imputation will be applied (i.e. baseline observation carried forward). Further for sensitivity, the effect that any missing data might have on results will be assessed via sensitivity analyses of augmented data sets.

(Insert Figure 4 around here)

Planned sensitivity analysis

Sensitivity analysis will be conducted to explore whether the degree of cartilage defects (score: 0-4), and plica presence (y/n) have any impact on the outcome after surgery. Furthermore, we will construct a dichotomous outcome on whole knee OA (y/n) to explore the effect of presence of knee OA. Whole knee OA will be defined as; participants with cartilage defects ICRS grade >2 in either of the patellofemoral, medial tibiofemoral or lateral tibiofemoral compartment excluding participants with TT (according to previous definition) and symptoms <6 months. In addition, the effect of differences in patient characteristics between groups reported in table 1 with a p-value less or equal to 0.10 will be tested in a fully adjusted model.

ETHICS AND DISSEMINATION
The Regional Scientific Ethics Committee of Southern Denmark has reviewed the outline of this cohort study. The committee waived the need for ethical approval as the study is only pertaining questionnaire and register data. Such studies can be implemented without permission from the Ethics Committee according to Danish legislation (Committee Act § 1, paragraph 1).

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

**DISCUSSION**

Arthroscopic meniscus surgery is high volume surgery[1]. Little is known about the natural time course of patient-reported outcomes after meniscus surgery and which factors affect these outcomes. This prospective cohort will collect data from a large number of patients on the natural time course of patient-reported outcomes prior and following arthroscopic meniscus surgery. Our results will enable analysis of the dependence of post surgery outcome on type of meniscus tear (i.e. TT vs. NTT in middle-aged patients). Further, it will be possible to investigate the dependence of post surgery outcome on type of surgery in the sub-group of patients with traumatic tears (i.e. TT$_{RES}$ vs. TT$_{REP}$). In contrast, other on-going randomized placebo controlled trials are investigating the effect of meniscus surgery for patients with degenerative tears [45, 46].

In this study a pragmatic clinical approach was chosen to categorize meniscus tears as either TT or NTT (i.e. degenerative). The advantages of this approach are that it is simple, cheap, can be determined prior to surgery (in contrast to histology or
arthroscopic observation), and feasible in a routine clinical setting. Thus, this information can be used to form an algorithm based on information available prior to surgery to select those patients who benefit most from surgery, which can be implemented in clinical practice. The definition of TT and NTT are similar but not identical to what has previously been used in other studies. Camanho et al. [12] divided patients into three groups; traumatic, degenerative and fatigue. In the present study the NTT group will include both degenerative and fatigue as defined by Camanho et al., as the focus of this study is on the traumatic versus non-traumatic initiation of the meniscal tear. Others have based their definition on sports participation [47].

A limitation to this study is that patients are included based on the main reason for surgery (i.e. suspicion of a meniscus tear). However, meniscus surgery may also be performed in relation to surgery for other knee pathologies. Those patients will not be included in the Knee Arthroscopy Cohort of Southern Denmark (KACS). This should be taken into account when interpreting the cohort data. On the other hand this makes it more likely that patient symptoms in the KACS cohort are primarily caused by the meniscus injury. Furthermore, we expect the age to be different in the TT compared to the NTT groups (i.e. NTT group being older), thus all statistical analysis will be adjusted for age. Nevertheless, this should still be taken into consideration when interpreting the results.

Meniscus surgery may not be the answer to improve patient perceived pain and function in all patients with meniscus tears. Different factors, such as type of tear, may affect the post-operative outcome. Ultimately the goal of this study is to improve
management of patients with meniscus tears through identifying factors associated with no or limited effect of surgery on patient-reported outcomes.

CONTRIBUTIONS

JBT and LSL conceived the study. All authors participated in the study design. JBT, RC and LSL drafted the manuscript. All authors participated in critical scrutinizing and revision of the manuscript and approved the final version.

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COMPETING INTERESTS

None
REFERENCES


Figure 1: Overview of collection of outcomes during the first year in the KACS cohort.
Figure 2: Overview of the recruitment flow in the KACS cohort.
Figure 3: Expected distribution per 450 patients recruited, divided by age, type of tear and type of surgery. NTT = non-traumatic tear, TT = traumatic tear, TT$_{RES}$ = traumatic tear resected, TT$_{REP}$ = traumatic tear repaired.
Figure 4: Overview of the full analysis set for study aim 1 and 2. NTT = non-traumatic tear, TT = traumatic tear, TT_{RES} = traumatic tear resected, TT_{REP} = traumatic tear repaired.
Knee Arthroscopy Cohort Southern Denmark (KACS):

Protocol for a prospective cohort study

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ABSTRACT

Background

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States. The procedure is considered trivial since conducted on an outpatient basis and patients leave the hospital a few hours after surgery. Little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and factors affecting these outcomes. A critical oversight of previous studies is their failure to account for the type of meniscal tear. Meniscus tears can be categorized as traumatic or non-traumatic. Traumatic tears are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint. Non-traumatic tears (i.e. degenerative tears) are typically observed in the middle-aged (35-55 years) and older population but the etiology is largely unclear. Knowledge about the potential difference in the effect of arthroscopic meniscus surgery on patient symptoms differs between patients with traumatic and non-traumatic tears is sparse. Furthermore, little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and factors affecting these outcomes. The aim of this prospective cohort study is to investigate the natural time course of patient-reported outcomes in patients undergoing meniscus surgery, with particular emphasis on the role of the type of symptom onset meniscus tear.

Methods/Design

This prospective cohort study enrol patients assigned for meniscus surgery. At baseline (PRE surgery), patient characteristics are assessed using an email-based questionnaire also comprising several validated questionnaires assessing general health, knee-specific characteristics and patient’s expectations of the surgery. Follow-
up will be conducted at 12 and 52 weeks after meniscus surgery. The major outcomes will be differences in changes, from before to 52 weeks after surgery, in each of the 5 domains on the Knee Injury and Osteoarthritis Outcome Score (KOOS) between patients undergoing surgery for traumatic compared with non-traumatic meniscus tears.

Dissemination

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

Trial registration number: ClinicalTrials.gov Identifier: NCT01871272

Key words: Cohort Study, Arthroscopy, Knee, Prospective Studies, Meniscus

Article focus

- This article describes a study protocol for a prospective cohort study investigating the natural time course of patient reported outcomes after arthroscopic meniscus surgery.

Key messages

- This study will provide information about the natural time course and potential difference in improvement in patient reported outcomes after arthroscopic meniscus surgery for traumatic and non-traumatic tears have particular emphasis on the importance of type of meniscus tear (i.e. traumatic or non-traumatic), which may have important implications for improvements in patients reported outcomes after surgery.

Strengths and limitations of this study

The KACS cohort study
This cohort study will provide information on the natural time course of patient reported outcomes in a clinical setting on a large group of patients after arthroscopic meniscus surgery to ensure high external validity.

As data is collected on a large number of patients in a clinical setting it was not feasible to collect standardized imaging data (i.e. MRI or radiographs) on patients, which could have provided valuable information. Patients with reconstruction of the anterior or posterior cruciate ligament will not be included in the KACS cohort.
INTRODUCTION

Meniscus surgery is high volume surgery carried out on 1 million patients annually in the United States [1] at an average cost of $5,000/procedure. The procedure is often considered trivial since conducted on an outpatient basis and patients leave the hospital few hours after surgery. Nevertheless, little is known about the natural time course of patient perceived pain, function and quality of life after meniscus surgery and which factors affect these outcomes [2]. The general opinion is that patients recover their muscle strength fully within 6-12 weeks following arthroscopic partial meniscectomy [3-5]. Importantly, however, recent studies have shown substantial patient-reported disability and pain in patients up to 4 years after surgery [6-8]. One explanation for the poor self-reported outcomes may be that the loss of meniscal function triggers other events that may cause knee pain [9]. Complicating the assessment of surgery effectiveness further, surgical procedures have shown to be associated with considerable “placebo effect”. Further, the “placebo effect” of arthroscopic surgery needs to be taken into account [10, 11] (Buchbinder). The general opinion is that patients recover their muscle strength fully within 6-12 weeks following arthroscopic partial meniscectomy [5-7]. Importantly, however, recent studies have shown substantial patient-reported disability and pain in patients up to 4 years after surgery [8-10]. A critical limitation of previous studies is their failure to account for the type of meniscal tear.

A critical limitation of previous studies [12-15] is their failure to account for the type of symptom onset (i.e., injury mechanism) meniscal tear. Meniscus tears can be categorized as either traumatic or non-traumatic. Traumatic tears (TT) are usually observed in younger, active individuals in an otherwise ‘healthy’ meniscus and joint,
and can be attributed to a specific incident (e.g. sports related trauma) [16]. TT’s are often associated with joint effusion, reduced knee joint range of motion (ROM) together with catching/locking of the knee. These ‘mechanical’ problems may be resolved with meniscus surgery (i.e. repair or resection). Non-traumatic tears (NTT) are typically observed in the middle-aged (35-55 years) and older population [17].

These tears are associated with meniscal calcification [18] and risk factors for these tears include; presence of Heberdens’s and Bouchard nodes, knee malalignment [19] and occupational kneeling [20], however the etiology is largely unclear [16]. NTT’s are often referred to as degenerative tears and have been shown are suggested to be associated with incipient knee osteoarthritis (OA) in the middle-aged or elderly population [21-23]. Evidence from four well-designed trials demonstrated that arthroscopic interventions [10, 24] and meniscectomy [25-27] were no better, or provided no additional effect, than the comparator (i.e. sham surgery, physical therapy or a combination of physical and medical therapy) to relieve pain and improve function in middle-aged patients with knee OA or early signs of knee OA. No corresponding randomized trials exist specifically for TT but an observational study showed that patients with degenerative meniscus lesions (i.e. NTT) self-report worse function and quality of life compared to individuals with traumatic tears at follow-up 14 years after meniscectomy [28]. Thus, it is conceivable, but currently unproven, that arthroscopic meniscus surgery is more effective in resolving symptoms of a meniscus tear of traumatic aetiology compared with non-traumatic tears in the middle-aged population.

In patients with TT, repair of the meniscus may be an alternative to resection. In contrast, repair is rarely an option for middle-aged patients with NTT due to the degenerative state of the meniscus. A recent retrospective observational study
suggested a reduced risk of later knee OA and less activity level loss in patients (~32 years at time of surgery) undergoing repair compared to resection (i.e. favoring repair) [29]. This indicates that patients with TT should be stratified into sub-groups on the basis of type of arthroscopic intervention (i.e. repair (TT\textsubscript{REP}) and resection (TT\textsubscript{RES})) since this may influence patient perceived outcomes after surgery.

Aims and hypotheses

The primary aims of this observational cohort are to:

(1) Investigate if improvements in patient self-reported pain, symptoms, function and quality of life differ after arthroscopic meniscus surgery for non-traumatic meniscus tears in middle-aged patients, compared with surgery in patients with traumatic tears (i.e., NTT vs. TT). We hypothesize that in middle-aged patients with NTT arthroscopic surgery is less effective in relieving self-reported pain, symptoms, function in sports and recreation and quality of life (i.e. change in KOOS scores), compared to younger patients undergoing surgery for TT.

(2) Investigate the effect of meniscus repair (TT\textsubscript{REP}) compared to meniscus resection (TT\textsubscript{RES}) on change in self-reported pain, symptoms, function in sports and recreation and quality of life in patients with TT. We hypothesize that arthroscopic surgery is less effective in relieving pain, symptoms, function in sports and recreation and quality of life (i.e., change in KOOS scores) in patients undergoing TT\textsubscript{RES} compared to those undergoing TT\textsubscript{REP}.

METHODS AND ANALYSIS

The KACS cohort study
Design

In this prospective cohort study we will assess patient-reported outcomes (PROs) using email-based questionnaires prior to surgery and at 12 and 52 weeks follow-up post surgery (see Figure 1).

(Insert Figure 1 around here)

Participants

All patients assigned for arthroscopy on suspicion of a meniscus tear at Lillebælt Hospital (located in the cities Vejle and Kolding, Denmark) and Odense University Hospital, Denmark (incl. Svendborg Hospital) from February 1st 2013 to January 31st 2014.

General cohort eligibility criteria:

Inclusion criteria: Patients ≥18 years of age assigned for arthroscopy on suspicion of a medial and/or lateral meniscus tear by the examining orthopaedic surgeon based on clinical signs and MRI (if available), having an email address and able to read and understand Danish.

Exclusion criteria: Patients who will or previously have undergone surgical reconstruction of the anterior or posterior cruciate ligament (ACL or PCL) in either knee, suffered fracture(s) to the lower extremities (i.e. hip, leg or foot) in either leg within the last 6 months at time of recruitment and patients not mentally able to reply the questionnaire. Please refer to Figure 2 for an overview of the recruitment flow.
Wide inclusion criteria are set to allow for later subgroup analysis. Patients with reconstructed ACL and PCL cannot be included as these patients are being followed in another cohort study.

Inclusion and exclusion criteria, aim 1 (NTT vs. TT):

There is no consensus on how to classify patients as having a NTT or TT. In this study, patients undergoing meniscus surgery will be classified as having either TT or NTT according to an algorithm based on age, duration of knee symptoms and one question about injury mechanism (see below). This represents the information that is available prior to surgery.

Injury mechanism question:

“How did the knee pain/problems for which you are now having surgery develop (choose the answer that best match your situation)?”

Response alternatives:

a. The pain/problems have slowly evolved over time

b. As a result of a specific incident (i.e. kneeling, sliding, twisting of the knee or the like)

c. As a result of a violent incident (i.e. during sports, a crash, collision or the like)

TT:
Inclusion: All patients between 18-34 years and all patients between 35-55 years replying “c” on the injury mechanism question.

NTT:
Inclusion: All patients between 35-55 years replying “a” or “b” on the injury mechanism question and having knee symptoms >6 months.

In addition, the general eligibility criteria also apply. For aim 1, the upper age limit is set to include patients with degenerative meniscus tears (i.e. NTT) but without severe features of knee OA [30]. Furthermore, patients which responses do not fit the TT and NTT criteria will also be excluded.

Inclusion and exclusion criteria, aim 2 (TT$_{RES}$ vs. TT$_{REP}$):

All patients classified as TT according to the specific KACS eligibility criteria for aim 1 will be further divided in patients having either meniscus resection (TT$_{RES}$) or repair (TT$_{REP}$) according to the type of surgery they receive to answer study aim 2.

Patient characteristics

At baseline, self-report information about: Educational level, employment, civil status, smoking habits, co-morbidities [31], physical activity level [32] and self-reported knee and foot alignment [33] will be collected together with information on height and weight. Surgery documentation will be collected using a modified version of the ISAKOS Classification of Meniscal Tears questionnaire[34], which is filled out...
by the operating surgeon. Additional surgery information not pertaining to the meniscus is also collected from surgery reports.

Major Outcomes

Knee Injury and Osteoarthritis Outcome Score (KOOS)  
All 5 domains (i.e., subscales) on the KOOS [35, 36] at the 1-year follow-up. The 5 KOOS domains are: pain, symptoms, function during daily activities (ADL), sport and recreational function (Sport/Rec) and quality of life (QOL). The KOOS score is ranging from 0-100 (0 indicating extreme symptoms and 100 indicating no symptoms). The KOOS score has been validated and previously used to assess self-reported outcomes in patients undergoing meniscus surgery [6, 8, 25, 27, 35, 36].

In addition, it has been shown to perform well in the entire continuum from very early changes of knee OA to knee arthroplasty [37]. All outcomes included in the study are listed in Table 1.

Minor Outcomes

Patient Acceptable Symptom State (PASS) and treatment failure (TF)  
One question regarding PASS will be used to assess how many patients consider themselves well after surgery (as opposed to feeling better) [38]. PASS is assessed as a dichotomous outcome (y/n) to the question: “Considering your knee function, do you feel that your current state is satisfactory? With knee function you should take into account all activities you have during your daily life, sport and recreational activities, your level of pain and other symptoms, and also your knee related quality of life”.

The KACS cohort study

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In addition, patients replying “no” to the PASS question will also be asked to answer (y/n) the following question: “Would you consider your current state as being so unsatisfactory that you think the treatment has failed?”. Patients replying, “yes” to the second question will be defined as experiencing “treatment failure” (TF).

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The SF-36 will be used to assess general physical function. The SF-36 consists of 8 subscales: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The SF-36 is self-explanatory, takes 10 minutes to complete, and is scored from 0–100 (0 indicating extreme problems and 100 indicating no problems). The Acute Danish version of the SF-36 was used [39, 40].

Table 1: Collection of patient characteristics, outcome measures and explanatory variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRE</th>
<th>Surgery</th>
<th>12 weeks</th>
<th>52 weeks</th>
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<td>Height</td>
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<tr>
<td>Weight</td>
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<td>Employment</td>
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<td>Co-morbidities</td>
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<td>Alignment</td>
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<tr>
<td>ISAKOS questionnaire</td>
<td></td>
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</tbody>
</table>
Knee joint stability X X X  
Expectations for surgery X  
SF-36 X X X  
KOOS X X X  
PASS X X  
TF X X  
GPE X X  
AE X X  

ISAKOS = International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine

(ISAKOS) Classification of Meniscal Tears questionnaire; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; KOOS = Knee Injury and Osteoarthritis Outcome Score; PASS = Patient Acceptable Symptom State; TF = Treatment Failure; GPE = Global Perceived Effect; AE = Adverse Events

Exploratory Outcomes

- Questions regarding patient expectations of surgery [41].
- Questions concerning knee joint stability/laxity. One question regarding frequency of symptoms and one question about the influence of symptoms (i.e. sense of instability during daily activities).
- Questions regarding postoperative rehabilitation (i.e. participation, type, frequency and degree of supervision).
- Questions regarding global perceived effect (GPE) to explore minimal clinical important change in patient-reported outcomes. GPE is evaluated on a seven-step global rating scale after surgery (ranging from better, an important improvement; somewhat better, but enough to be an important improvement;
very small change, not enough to be an important improvement; about the same; very small change, not enough to be an important worsening; somewhat worse, but enough to be an important worsening; worse, an important worsening). A two-step change in GPE is considered clinically important [42].

Adverse events (AE)

Adverse events (not necessarily implying causality to the surgery), defined as self-reported symptoms after surgery causing limitations in daily activities, sport and recreational activities or work limitations together with symptoms causing patients to seek medical care or having re-surgery will be collected by self-report and patient record review.

Data management

All self-reported data are collected using email-based questionnaires. Participant submitted responses are automatically registered in a secured database. At all data collection points an email reminder is send to participants if they do not answer the email-based questionnaire with-in 3-4 days. In addition, participants who do not reply after the reminder will be called by phone to ensure a high follow-up rate.

Information registered by surgeons on the modified ISAKOS questionnaire following surgery will be transferred from paper format to electronic format using Automated Forms Processing. This method is a validated alternative to double entry of data [43].

Statistical analysis
The cohort will recruit all eligible patients from February 1st 2013 to January 31st 2014. Conservatively estimated we expect to recruit 450 patients to the KACS cohort within this timeframe. For an overview of the expected distribution of patients recruited between 18 and 55 years, please refer to Figure 3.

The minimal clinically important change (MCIC) on the KOOS subscale is considered to be 8-10 points [37]. Thus, with the estimated recruitment flow and distribution (Figure 3) we will have a power of 0.99 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean difference of 8 KOOS points between NTT and TT (primary study aim 1).

In addition, we will have a power of 0.88 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P less or equal to 0.05), assuming a common standard deviation of 15 KOOS points to detect a mean difference of 10 KOOS points between TTRES and TTREP (study aim 2).

If we are not able to reach sufficient numbers within the one year timeframe, recruitment will continue until the numbers specified in the a priori sample size calculation are reached.

*(Insert Figure 3 around here)*

Descriptive results will be given as means with standard deviations (or medians with interquartile range) and as percentages. Between-group comparisons of the KOOS and SF-36 scores at the 52 weeks follow-up will be analyzed with the use of ANalysis of COVariance (ANCOVA), stratified by site and adjusted for the preoperative score level, sex, age, and BMI. PASS and TF will be analysed using chi-square test.
Multiple logistic regression will be applied to estimate odds ratios for dichotomous outcomes. Mixed linear effects models with patient as random factor and sex, age and BMI as fixed factors will be used to explore change over time (i.e. baseline, 12 weeks and 52 weeks follow-up) in KOOS and SF-36 scores. Results will be presented with 95% confidence intervals. No interim analysis will be performed. All reported P values are two-sided and will not be adjusted for multiple comparisons. All data analyses will be carried out according to the pre-established analysis plan. All descriptive statistics and tests will be reported in accordance to the recommendations of the ‘Enhancing the QUAlity and Transparency Of health Research’ (EQUATOR) network: the STROBE statement[44].

Full analysis set

To qualify for the “full analysis set” recruited patients must reply to the baseline questionnaire and have surgery performed to their meniscus. Please refer to Figure 4, for an overview of the full analysis set. In case of missing data a non-responder imputation will be applied (i.e. baseline observation carried forward). Further for sensitivity, the effect that any missing data might have on results will be assessed via sensitivity analyses of augmented data sets.

(Insert Figure 4 around here)

Planned sensitivity analysis

Sensitivity analysis will be conducted to explore whether the degree of cartilage defects (score: 0-4), and plica presence (y/n) have any impact on the outcome after
surgery. Furthermore, we will construct a dichotomous outcome on whole knee OA (y/n) to explore the effect of presence of knee OA. Whole knee OA will be defined as; participants with cartilage defects ICRS grade >2 in either of the patellofemoral, medial tibiofemoral or lateral tibiofemoral compartment excluding participants with TT (according to previous definition) and symptoms <6 months. In addition, the effect of differences in patient characteristics between groups reported in table 1 with a p-value less or equal to 0.10 will be tested in a fully adjusted model.

ETHICS AND DISSEMINATION

The Regional Scientific Ethics Committee of Southern Denmark has reviewed the outline of this cohort study. The committee waived the need for ethical approval as the study is only pertaining questionnaire and register data. Such studies can be implemented without permission from the Ethics Committee according to Danish legislation (Committee Act § 1, paragraph 1).

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences.

DISCUSSION

Arthroscopic meniscus surgery is high volume surgery[1]. Little is known about the natural time course of patient-reported outcomes after meniscus surgery and which factors affect these outcomes. This prospective cohort will collect data from a large number of patients on the natural time course of patient-reported outcomes prior and following arthroscopic meniscus surgery. Our results will enable analysis of the
dependence of post surgery outcome on type of meniscus tear (i.e. TT vs. NTT in middle-aged patients). Further, it will be possible to investigate the dependence of post surgery outcome on type of surgery in the sub-group of patients with traumatic tears (i.e. TT\textsubscript{RES} vs. TT\textsubscript{REP}). In contrast, other on-going randomized placebo controlled trials are investigating the effect of meniscus surgery for patients with degenerative tears [45, 46].

In this study a pragmatic clinical approach was chosen to categorize meniscus tears as either TT or NTT (i.e. degenerative). The advantages of this approach are that it is simple, cheap, can be determined prior to surgery (in contrast to histology or arthroscopic observation), and feasible in a routine clinical setting. Thus, this information can be used to form an algorithm based on information available prior to surgery to select those patients who benefit most from surgery, which can be implemented in clinical practice. The definition of TT and NTT are similar but not identical to what has previously been used in other studies. Camanho et al. [12] divided patients into three groups; traumatic, degenerative and fatigue. In the present study the NTT group will include both degenerative and fatigue as defined by Camanho et al., as the focus of this study is on the traumatic versus non-traumatic initiation of the meniscal tear. Others have based their definition on sports participation [47].

A limitation to this study is that patients are included based on the main reason for surgery (i.e. suspicion of a meniscus tear). However, meniscus surgery may also be performed in relation to surgery for other knee pathologies. Those patients will not be included in the Knee Arthroscopy Cohort of Southern Denmark (KACS). This should be taken into account when interpreting the cohort data. On the other hand this
makes it more likely that patient symptoms in the KACS cohort are primarily caused by the meniscus injury. Furthermore, we expect the age to be different in the TT compared to the NTT groups (i.e. NTT group being older), thus all statistical analysis will be adjusted for age. Nevertheless, this should still be taken into consideration when interpreting the results.

Meniscus surgery may not be the answer to improve patient perceived pain and function in all patients with meniscus tears. Different factors, such as type of tear, may affect the post-operative outcome. Ultimately the goal of this study is to improve management of patients with meniscus tears through identifying factors associated with no or limited effect of surgery on patient-reported outcomes.

CONTRIBUTIONS

JBT and LSL conceived the study. All authors participated in the study design. JBT, RC and LSL drafted the manuscript. All authors participated in critical scrutinizing and revision of the manuscript and approved the final version.

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None
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