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Epidemiology of meniscus position: associations with knee symptoms and osteoarthritis

Fredrik Svensson

DOCTORAL DISSERTATION

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Abstract

Meniscal extrusion (ME) in the knee joint is defined as when the peripheral border of the meniscus is substantially located outside the joint margin. Prior studies have reported that ME is associated with meniscal tears, meniscal degeneration, and the presence of knee osteoarthritis (OA). Medial ME of the body of 3 mm or more, as seen on knee Magnetic Resonance Imaging (MRI) has a wide acceptance to be regarded as “pathologic”. However, it is still unclear if ME is associated with knee pain. My aims with this thesis were to: *i)* study the normal ME with its change over time and its relationship with meniscus tear/damage in knees without OA; *ii)* to scrutinize the widely accepted 3 mm cut-off for “pathological” medial ME; *iii)* determine an optimal cut-off for ME associated with radiographic knee OA, bone marrow lesions (BMLs) and cartilage damage; and *iv)* investigate the association between medial ME and pain in knees without radiographic OA.

In paper I we used 118 subjects from the Osteoarthritis Initiative (OAI) “non-exposed” reference cohort (aged 45-79 years, free of knee pain, radiographic knee OA and risk factors for knee OA) and in papers 2-4 1004 subjects from the community based Framingham Osteoarthritis Study (aged 50–90 years, selection not made on the basis of knee problems). MRI´s were read for ME, cartilage coverage, BMLs and cartilage damage. Knee x-rays were read according to the Kellgren and Lawrence scale. I estimated changes in ME over 4 years using repeat knee MRI. I evaluated the 3 mm cut-off and estimated a new cut-off for “pathologic” extrusion. The odds ratio (OR) for pain as outcome, with ME as exposure was estimated and adjusted for age, sex, body mass index, meniscal tear, BMLs, cartilage damage and previous knee injury as confounders.

In the OAI-cohort we found only minor increase in medial ME over 4 years. In the Framingham cohort ME was on average 2.7 mm medially and 1.8 mm laterally. Cartilage coverage was about 30% of ipsilateral cartilage surface. Meniscal damage was associated with more ME medially. A new estimated 4 mm cut-off maximizes the sum of sensitivity and specificity for the OA features radiographic OA, BML and cartilage damage. The OR for knee pain was 1.15 (95% confidence interval 0.97, 1.37) per 1 mm more ME, indicating only a weak association with pain.

In conclusion my thesis delivers an array of novel normative data for meniscus body position on MRI, as well as its associations with meniscal damage and knee OA. Medial ME is strongly associated with knee OA. The cut-off value 4 mm may be a more optimal cut-off to use than 3 mm to be considered ”pathologic”. Further, medial ME *per se* seems to have a weak association with pain in knees free of radiographic OA..

Key words: Bone marrow lesion, cartilage damage, coverage, knee joint, magnetic resonance imaging, meniscal extrusion, meniscal tear, meniscus, osteoarthritis, pain

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Contents

Summary

Background and aims

Meniscal extrusion (ME) on knee magnetic resonance imaging (MRI) is strongly associated with knee osteoarthritis (OA) and medial ME ≥3 mm on MRI is often considered a threshold for "pathological" extrusion. However, there is a lack of information regarding meniscal position in the general population, in the asymptomatic knee and its change over time. It is still unclear if ME alone is linked with knee pain. The aims of this study were: 1) to study meniscal body position and its change over 4 years in asymptomatic adults; 2) to determine ME and cartilage coverage on MRI and associated factors in knees of middle-aged and elderly persons free from radiographic OA; 3) scrutinize the 3 mm as cut-off for "pathological" medial ME; 4) find an optimal cut-off for ME associated with radiographic knee OA, bone marrow lesions (BMLs) and cartilage damage; and 5) investigate the association between medial ME and pain in knees free of radiographic OA.

Methods

For the first aim we used data from the Osteoarthritis Initiative (OAI) and studied both knees from 118 subjects (mean age 55 years) from the OAI "non-exposed" reference cohort free of knee pain, radiographic knee OA and risk factors for knee OA. We assessed mid-coronal intermediate-weighted 3-Tesla magnetic resonance images from baseline and at the 2- and 4-year follow-up visit. We measured tibia plateau, meniscal body width and meniscal body extrusion in both compartments. We calculated meniscal overlap distance on the tibial plateau, % coverage, and extrusion index compared to tibia width. Trends in position over the 4-year period were evaluated using a linear mixed-effects regression model.

For aim 2-5 we used 1004 subjects aged 50–90 years from the Framingham Community cohort. We measured medial and lateral ME and cartilage coverage on 1.5 T MRI of both knees. We also determined meniscal morphology and structural integrity. The multivariable association with age, body mass index (BMI), and ipsilateral meniscal damage was also evaluated. BMLs and cartilage damage were

read using the whole organ magnetic resonance imaging score (WORMS). We evaluated the 3 mm cut-off with respect to radiographic OA, BML and cartilage damage. Then a new cut-off maximizing the sum of sensitivity and specificity was calculated. The subjects were asked about knee pain in the last month. We estimated the odds ratio (OR) and difference in prevalence for pain as outcome and medial ME as exposure. The model were adjusted for age, sex, body mass index, meniscal tear, bone marrow lesions, cartilage damage and previous knee injury as potential confounders. Further, knees from each individual discordant for knee pain were evaluated in a paired (matched) analysis to adjust for person-level confounding.

Results

In paper I the mean (SD) values at baseline for medial ME and overlap distance were 1.64 mm (0.92) and 10.1 mm (3.5), and coverage was 34.4% (11.9). The corresponding values for the lateral compartment were 0.63 mm (0.73), 9.8 mm (2.4), and 31.0% (7.7). Medial ME index was greater in female knees (p = 0.03). There was slight increase in medial meniscal body extrusion over 4 years (0.040 mm/year [95% CI: 0.019-0.062]). The other variables were relatively stable.

In paper II mean ME was medially 2.7 mm and laterally 1.8 mm. The tibial cartilage coverage was about 30% of ipsilateral cartilage surface (both compartments). Ipsilateral meniscal damage was associated with more ME medially.

In paper III, knees with radiographic OA, BMLs and cartilage damage had overall more ME than knees without. A new 4 mm cut-off had a better sum of sensitivity and specificity and improved the percentage of correctly classified subjects.

The OR for reporting any knee pain in the last month controlled for all included confounders was 1.15 (95% confidence interval 0.97, 1.37) per 1 mm more extrusion. The paired analysis yielded similar results (Paper IV).

Table 1: Mean medial meniscal extrusion (SD) in mm, both knees, both used datasets. NA = not available.

		Mean medial meniscal extrusion	
Dataset		Right knee	Left knee
OAI	all knees	1.9 (1.0)	1.4 (0.8)
	with meniscal tear	1.9 (0.8)	2.1 (1.0)
Framingham	all knees	2.6 (1.2)	2.8 (1.1)
	with meniscal tear	4.0 (1.9)	NA
	without pain	2.5 (1.2)	2.8 (1.2)
	with frequent pain	2.8 (1.2)	2.9 (1.3)

Conclusions

In asymptomatic adults, the relative degree of ME is more pronounced in female knees. Although a slight increase in medial ME over time was noted, positions were relatively stable within subjects over time. Mean medial ME in middle-aged or older persons without radiographic knee OA approximates the commonly used cut-off (3 mm) to denote pathological ME. Medial meniscal damage is a factor associated with medial ME and less cartilage coverage. The cut-off 4 mm may be used as an alternative cut-off for denoting pathological ME. Moderate medial ME *per se* seems to have a weak association with pain in knees free of radiographic OA and it probably only explains a minor part of the subjects' knee pain.

Original papers

I. Meniscus body position and its change over four years in asymptomatic adults: a cohort study using data from the Osteoarthritis Initiative (OAI). Bruns K, Svensson F, Turkiewicz A, Wirth W, Guermazi A, Eckstein F, Englund M. BMC Musculoskelet Disord. 2014 Feb 5;15:32. doi: 10.1186/1471-2474-15-32.

II. Meniscal body extrusion and cartilage coverage in middle-aged and elderly without radiographic knee osteoarthritis. Svensson F, Felson DT, Zhang F, Guermazi A, Roemer FW, Niu J, Aliabadi P, Neogi T, Englund M. Eur Radiol. 2018 Oct 2. doi: 10.1007/s00330-018-5741-3. [Epub ahead of print]

III. Scrutinizing the cut-off for "pathological" meniscal body extrusion on knee MRI.
Svensson F, Felson DT, Turkiewicz A, Guermazi A, Roemer FW, Neuman P, Englund M. (in press Eur Radiol)

IV. Meniscal body extrusion and the association with knee pain.
Svensson F, Felson DT, Turkiewicz A, Guermazi A, Roemer FW, Neuman P, Englund M (in manuscript)

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Paper I:

Conception and design: Martin Englund, Felix Eckstein.

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Analysis and interpretation of the data: Katharina Bruns, Fredrik Svensson, Aleksandra Turkiewicz, Wolfgang Wirth, Ali Guermazi, Felix Eckstein, Martin Englund.

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Abbreviations

AUC = Area under the curve

BLOKS = Boston Leeds Osteoarthritis Knee Score

BML = Bone Marrow Lesions

ECM = extracellular matrix

IKDC = International Knee Documentation Committee

JSN = Joint space narrowing

KL = Kellgren and Lawrence

KOSS = Knee Osteoarthritis Scoring System

LMCEx = lateral meniscal coronal extrusion

LMCW = lateral meniscal coronal width

LTPW = lateral tibia plateau width

MMCEx = medial meniscal coronal extrusion

MMCW = medial meniscal coronal width

MME = Medial meniscal extrusion

MOAKS = MRI Osteoarthritis Knee Score

MRI = Magnetic Resonance Imaging

MTPW = medial tibia plateau width

OA = Osteoarthritis

OAI = Osteoarthritis Initiative

TW = tibial width

WOMAC = Western Ontario McMaster University arthritis index

WORMS = Whole Organ Magnetic Resonance imaging Score

Introduction

Osteoarthritis in the knee

Osteoarthritis (OA) in general is the most common chronic condition of the joints[1]. It is also one of the most common reasons of global disability and its overall prevalence is increasing[2 3]. OA can affect any joint, but the knee is one of the most effected sites[4]. Age is a strong risk factor for knee OA and hence most people with the disease are middle aged or older[5-7]. This doesn´t necessarily imply that knee OA is only "wear and tear" that appears with age. The cause is more complex and OA should be seen as a real disease with many different phenotypes. In short the cause is a multifactorial interaction of genetic predisposition, mechanical factors, inflammation and ageing[5 7-11]. A common definition for OA is: "a heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins"[12]. Knee OA in early ages often has a genetic component, such as inadequate collagen in the cartilage or malalignment of the knee[13-15]. Overweight with excessive adipose tissue is associated with increased cartilage loss and production of pro-inflammatory cytokines[16]. Being overweight puts additional pressure on the knees. Many years of carrying extra weight can cause the cartilage in the joint to break down faster. Injuries to the knee joint such as a fractures or sprains increase the risk for OA[5]. Therefore OA in young adults often have a history of trauma to the affected knee. Having a work that requires standing for long periods of time, repetitive bending, heavy lifting has also been reported to increase the OA risk[17]. Other more uncommon factors may contribute to osteoarthritis. These factors include systemic disorders like gout, synovitis, metabolic disorders such as haemophilia and acromegaly[18].

The most common symptoms of knee OA are pain and stiffness, especially after some rest or in the morning. Swelling of the joint can occur due to increased amount of joint fluid and synovitis. This symptom is more common after mechanical overload and inflammation.

Knee pain can lead to a sedentary lifestyle and increases the risk for obesity[19]. Being obese can lead to the effects metabolic syndrome, such as diabetes, high blood pressure and coronary heart disease. Knee pain due to knee OA is a very common reason for seeking medical care and knee arthroplasty, the end stage treatment, is one of the most common orthopaedic surgeries. In this context, the need for understanding, prevention and correct treatment of knee OA is essential. The aim of this work has been to add another piece in the OA puzzle.

The meniscus

The normal meniscus

The term meniscus comes Greek meniskos (crescent moon). The human knee joint has two fibrocartilaginous semi-lunar menisci. Looking at them one finds a glossy smooth, lubricated tissue located inside the joint. Their shapes fill out the gap between femur and tibia. They consist of a complex tissue comprised of cells, specialized extracellular matrix (ECM) molecules, innervation and vascularization (only peripheral part in adults). Since the articular surface of femur is round and convex, the superior side of the menisci are concave. The surface of tibia is almost flat and so are the corresponding surfaces of the menisci. In a cross section the meniscus has close to a triangular shape, with the thinner slice pointing towards the joint and the thicker edge towards the joint capsule. The menisci differ in shape and size. The lateral meniscus is almost circular. The medial meniscus is C-shaped and bigger. It covers a larger portion of the articular surface and absorbs a larger portion of forces through the menisci[20 21]. Both the anterior and posterior horn of the menisci are strongly attached in connection to the intercondylar fossa[22 23]. Through its strong connection to the joint capsule and medial collateral ligament the medial meniscus is firmly attached to the femur. The lateral meniscus is loosely attached to the capsular ligament and is thereby more mobile. A fibrous band, the transverse ligament, connects the anterior edges of both menisci[24]. The meniscofemoral ligaments (Humphrey and Wrisberg) connect the posterior horn of the lateral meniscus near the femoral insertion site of the posterior cruciate ligament. There is a big inconsistency in the actual appearance of these to ligaments.

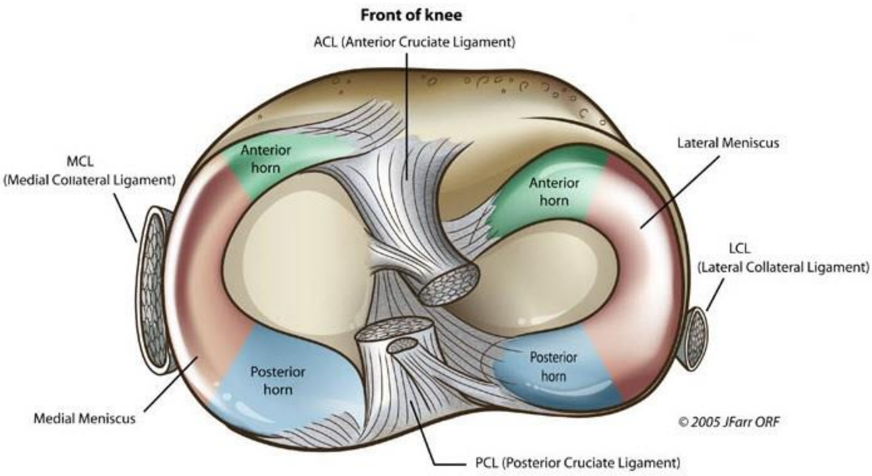

Figure 1: Picture inside of the knee seen from above shoving tibial plateau, menisci and ligaments.

The meniscus cells originate from the same cell type of the mesenchymal tissue. Later in the development they differentiate and look like different cell types depending on the localization in the meniscus. Characterizations of meniscus cells in the literature are inconsistent and still a topic of controversy[25]. Terms like fibrocytes, fibroblasts, meniscus cells, fibrochondrocytes, and chondrocytes are used. Easy explained are the outer cells fibroblast-like and the matrix surrounding them mainly consists of type I collagen. The cells of the inner portion are more chondrocyte-like cells with an ECM mainly of type II collagen mixed with a small amount of type I collagen[26]. At the surface the menisci have a random collagen fibrillary network, circumferential collagen bundle fibres and additionally we find radially oriented connecting fibres. Apart from collagen the ECM of the meniscus consists approximately to 70 % of water. Further we find proteoglycans, non-collagenous proteins, and glycoproteins.

Knowledge of the meniscal vascularization is important to understand meniscal pathologies. The medial, lateral, and middle geniculate arteries are the major blood suppliers[27]. Originally in the prenatal development the whole meniscus is vascularized. Until adulthood the vascularization constantly decreases and the meniscus turns into a relatively avascular structure, leaving only the peripheral 10% - 30% of the medial meniscus border and 10% - 25% of the lateral meniscus well vascularized. Hereby two zones of the meniscus can be distinguished: the outer, vascularized red zone and the inner avascular white zone. The avascularised zone depend on nourishment from the synovial fluid via diffusion or mechanical pumping due to joint motion. Apparently, the healing capacity of the red zone is superior to the white zone[28].

Innervation of the knee joint and the menisci derives mainly from the tibial nerve. Nerve fibres penetrate the joint capsule and follow the vascular supply of the menisci in peripheral portion of the menisci[29 30]. The anterior and posterior horns are richer innervated then the mid portions[31]. Three types of mechanoreceptors are found in the menisci (Ruffini, Pacinian and Golgi)[32 33]. The density of these structures is higher in the meniscal horns, above all in the posterior horn. The meniscus has many biomechanical functions. It contributes to shock absorption, to disperse the weight of the body, to reduce friction during movement, to load distribution, enhance joint stability, lubrication and proprioception[34 35]. About 70% of the load passes through the medial tibiofemoral compartment and 30% through the lateral compartment. Since the menisci enhance the contact area in the knee, they transmit over 50% of the total axial load trough the joint[36-38]. During flexion and mechanical stress the shape and position of the menisci changes. The lateral meniscus, being more mobile, shows a greater range of motion. The medial meniscus have lesser excursions during joint load and is thereby more prone to injuries[39]. The mainly axial force in the knee joint is conversed into circumferential force, “hoop stress”, inside the menisci. The collagen fibre distribution and orientation is well adapted for this mechanical role. The rigid fixations of the anterior and posterior horns prevent the meniscus from extruding peripherally during load bearing.

As all other tissues, the meniscus alters with age. With increasing age the meniscus becomes stiffer and loses its glossy surface. Not only is the red zone smaller in higher ages, but also the cell structure and ECM changes over time. The amount of elastic tissue decreases and fibrous tissue increases. The collagen density increases until 30 years of age and is apparently declined after 80 years of age[40].

Meniscal pathology

Meniscal lesions are the most common intra-articular knee injuries. The cause and type of lesion differs in different age groups[41]. In children and young adults the main mechanism is meniscal tearing due to trauma from sports[20 42]. Typically twisting of the knee in a flexed position or hyperextension overloads the durability of the meniscus. The classification normally distinguishes between red zone and white zone lesions, where the latter have the worst healing potential[30]. The medial meniscus is more prone to damage, probably due to its more rigid fixation[43 44]. In the middle aged and older population meniscal tears typically come from degeneration of the menisci, often without any known trauma to the knee. In this age category there is an overrepresentation of simultaneous knee OA. The literature shows that degenerative meniscal tears are associated with both radiographic and symptomatic knee OA[45-58]. Meniscal tears as such have for a long time been believed to typically cause pain and therefore been treated with surgery. This theory has recently been challenged and many authors suggest that degenerative meniscal tears are on the knee OA causal pathway [49 59]. Thereby the prevalence of meniscal tears is higher in the older population. Englund et al reported that 61 % of the subjects who had meniscal tears had not had any pain, aching, or stiffness during the previous month[60]. Apart from age and trauma, obesity is reported to be a risk factor for meniscal pathology[61].

Meniscal extrusion

The definition for meniscal extrusion is when the peripheral border of the meniscus extends beyond the tibial margin. In the literature it's also referred to as meniscal subluxation or radial displacement[51 62 63]. Due to its intended function, the meniscus is supposed to change shape and position during weight bearing[21 35 64]. Therefore some degree of meniscal extrusion is physiological[65]. One of the main topics in this work has been to distinguish between "normal" and pathological meniscal extrusion. The question whether meniscal extrusion is the result of an increasingly mobile meniscus, laxity of joint capsule and ligaments, and/or if the extrusion and displacement is a result of an already damaged meniscus is still to be answered. Many studies, among them paper I, are leaning towards the latter theory[43 47 51 54 64]. This means that meniscal extrusion is the result from tearing of collagen fibres within the meniscus that provide hoop strength. Tearing of the meniscus is a known factor related to meniscal extrusion[43 47 51 54 64 66]. Root tears are by many authors considered as the most important factor associated with extrusion of the meniscus and quite often the reason for surgical treatment[67-69]. An extruded and teared meniscus loses the ability to resist hoop stress and biomechanically this leads to an overload of joint articular surfaces. It has been reported that meniscal extrusion is an independent predictor of tibiofemoral cartilage loss and degenerative subchondral bone marrow lesions (BML), ultimately contributing to progression of knee OA[70]. The literature also shows that meniscal extrusion is highly associated with symptomatic knee OA[54 57 71].

Other factors reported to be associated with meniscal extrusion are malalignment, female gender, knee injury and cartilage damage[47]. Obesity should logically accelerate the meniscal overload and thereby lead to displacement, but the literature is somewhat inconsequent in this matter[51 65 72]. This was also something we in this work wanted to investigate.

At which degree is the meniscal extrusion pathologic? Gale et al in 1999 stipulated that medial meniscal body extrusion of 3 mm or more was suggested to be pathologic[51]. However, different MRI-scores grade the meniscal extrusion different (see below). What to be seen as “normal” or pathological meniscal extrusion is still to be scrutinized.

Diagnosis

The prime diagnostic tools for identifying either meniscal alterations or knee OA are a thorough medical history and clinical examination.

Typical symptoms for knee OA are pain, stiffness, reduced range of movement, joint instability and swelling[73]. Advanced arthritis may create a “scraping” sensation (crepitus) when moving the knee. Joint effusion can occur, but is sometime hard to assess[74]. A trained physician can get a good overview of patient’s complaints and typically no other diagnostic tools are needed. The combination of medical history, symptoms and clinical examinations gives a sensitivity of 95 % and a specificity of 69 %[75]. Meniscal injuries in the young often have a sudden onset, mostly in combination with some kind of trauma or overload. These patients typically have a distinct pain in one knee compartment, sometimes with limited range of movement due to pain or catching. They can present positive meniscal tests like McMurray´s test or Apley´s Grind. It should be mentioned, that no meniscal test alone is precise for the diagnosis of a meniscal tear[76] tear[76] (ref Snoeker A clinical prediction rule for meniscal tears in primary care). In older people, since the meniscal damage often is due to a degenerative meniscus, the history and examination is often not as clear. In these patients the cause of knee pain often cannot be distinguished between knee OA, meniscal damage and other knee conditions[77]. It is still unclear if meniscal extrusion alone is associated with knee pain and therefore thought to be investigated in paper 4. Some kind of imaging of the knee is occasionally inevitable for more precise diagnosis of structural alterations[78].

X-ray

Although plain radiographs of the joint are not necessary to diagnose knee OA they are widely used, for instance to monitor the progression of OA. There are different classification systems for grading of OA in the knee. The Ahlbäck system, founded in 1968, has been found to have comparable interobserver reliability to the newer International Knee Documentation Committee (IKDC) [79-83]. The biggest advantage with the Kellgren and Lawrence (KL) system is the common use as a research tool in epidemiological studies. This classification was proposed by Kellgren et al. in 1957 and uses a five grade scale[84]. (Table 2). It is supposed to describe the radiological changes after meniscectomy. Kenny et al concluded interestingly that radiographic signs of knee OA known to follow meniscectomy can develop in knees with significant extrusion of the medial meniscus[63]. The Brandt and Jäger-Wirth classifications, as most others, focus on joint space narrowing. No single radiographic classification system for OA is superior in interobserver reliability. In our work we used the Kellgren and Lawrence (KL) classification, since it is the most-studied classification system[85]. Previous reports demonstrate a wide range of interobserver reliability (0.51 to 0.89)[79 82-85]

Table 2: The Kellgren and Lawrence system

	The Kellgren and Lawrence system
Grade 0	No radiographic features of OA are present
Grade 1	Doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2	Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

The best results are produced using the Rosenberg view (the 45° posteroanterior flexion weight bearing radiograph) instead of plain AP radiographs[79 86]. Plain radiographs are a quite good tool for detecting knee OA, but normally meniscal pathologies or other features such as BMLs and cartilage damage are not shown with x-ray technique. This may require the use of magnetic resonance imaging (MRI). In contrast it has been shown, that initial joint space narrowing on plain radiographs can be secondary to meniscal extrusion rather than thinning of articular cartilage[45].

Magnetic Resonance Imaging

This is the ideal modality for imaging of soft tissues in and around the knee joint. MRI visualises most components of the joint, including articular cartilage, menisci, intra-articular ligaments, synovium, bone marrow, subchondral cysts, synovial plicae and vascular variants[87-90]. MRI is very sensitive for intra-articular lesions that are not detectable by radiography[53 91-93]. The excellent spatial resolution, tissue contrast, and multiplanar capability make MRI an excellent tool for assessment of articular cartilage[94]. Therefore it plays an important role both in a clinical setting and in research. MRI could in some cases be seen as "oversensitive", showing incidental findings in otherwise asymptomatic people[53 60]. MRI has for a long time been seen as expensive and in many countries the access is still insufficient. Another drawback with MRI is the narrow cavity, causing problems for people with claustrophobia and obesity. In order to achieve perfect images, the patient has to lie still for some time. MRI artefacts leading to pitfalls in meniscal assessment include motion artefacts[95]. Metallic implants close to the investigated joint often impair the image quality. Mostly the patients are placed in a supine position, whereupon the images are without weight bearing. This obviously alters the perception of joint space narrowing and meniscal extrusion. Identification of meniscal tears is mostly based on two criteria: intrameniscal signal exiting the superior or inferior articular surface of the meniscus and change in morphology of the meniscus[96 97]. However, evaluation of menisci may be challenging and it may sometimes be difficult to distinguish tears from areas of intrameniscal degeneration.

Magnetic resonance imaging (MRI) based semi-quantitative scoring of knee OA is established method for performing multi-feature joint assessment in observational studies of OA[98].The most known and used scoring systems for the knee are the Boston-Leeds Osteoarthritis Knee Score (BLOKS), the MRI Osteoarthritis Knee Score (MOAKS), the Knee Osteoarthritis Scoring System (KOSS) and the Whole Organ MR Score (WORMS)[99-103]. Features scored the in the different systems are among others: bone marrow lesions, cartilage quality, osteophytes, meniscal tears and meniscal extrusion/subluxation. In all four papers we used the WORMS. It was originated in 2004 and has been used in many observational studies and has a high inter-observer agreement among trained readers[102 103].

Aims of the study

General aim

To investigate the normal meniscus position in a general population, in different ages and how is it related to meniscus tears, radiographic OA and symptoms.

Specific aims

To describe the natural history of meniscus position in asymptomatic adults. (Paper I)

To describe the normal range of meniscus position and its relationship with meniscus tear in knees without OA in the general population. (Paper II)

To estimate an optimal cut-off for meniscal extrusion associated with radiographic knee osteoarthritis, bone marrow lesions (BMLs) and cartilage damage. Is there a cut-off value for meniscal extrusion where the meniscus is at risk? (Paper III)

To investigate association between medial meniscal extrusion and pain in knees free of radiographic OA. (Paper IV)

Methods

OAI

The Osteoarthritis Initiative (OAI) is a multi-centre, longitudinal, prospective observational study of knee OA. Purpose of the OAI is to provide a public domain research source, to enable the scientific evaluation of biomarkers for OA. The study is expected to improve the understanding of how modifiable and non-modifiable risk factors are linked to development and worsening of knee OA.

Four clinical centres and a data coordinating centre, conduct the Osteoarthritis Initiative (OAI), all located in the US. All four clinical centres have one 3.0 Tesla MRI scanner dedicated to imaging the knees of OAI participants annually over four years.

The OAI cohort consists of 4,796 participants, 58% women and ranged in age from 45-79 at time of recruitment, enrolled between February 2004 and May 2006. The OAI preserve a natural history database for OA that consist of clinical evaluation data, x-ray images, MRI and a bio specimen (serum, plasma, urine, and DNA).

The OAI consortium receives public funding from the National Institutes of Health (NIH) and private funding from several private company partners managed by the Foundation for the National Institutes of Health. The OAI was approved by the institutional review board for the University of California, San Francisco (UCSF) and its affiliates.

Public access is available at http://www.oai.ucsf.edu/.

Paper I was based on the “non-exposed” sub cohort of the OAI. This cohort consists of 122 subjects (47 men and 75 women; age range: 45-79 years). Purpose of the sub cohort is to distinguish biomarkers that are specific for knee OA and characterize distributions in normal subjects. Descriptive statistics of the study sample in Paper I are listed in table 3.

Inclusion criteria were:

- No pain, aching or stiffness in either knee in the past year;
- No radiographic OA in the tibiofemoral joint of either knee;
- No eligibility risk factors for knee OA present with the exception of age ≥ 70 years.

In brief, the eligibility risk factors were: certain knee symptoms associated with OA in the past 12 months, overweight, history of knee injury and/or knee surgery, family history of total knee replacement, Heberden's nodes in both hands, repetitive knee bending, and age 70-79 years).

Table 3: Descriptive statistics of the study sample in Paper I.

Characteristic	N=118
Women, n (%)	72 (61)
Age, mean (SD) *years*	55.0 (7.5)
Body mass index, mean (SD) *kg/m²*	24.4 (3.2)
Kellgren and Lawrence grade, n (%)*	
0	99 (85)
1	17 (15)
Medial meniscal tear, n (%)	
Right knee	9 (7.6)
Left knee	8 (6.8)
Lateral meniscal tear, n (%)	
Right knee	6 (5.1)
Left knee	3 (2.5)

* missing data for 2 subjects

Framingham Osteoarthritis Study

The Framingham Osteoarthritis Study consists of a random sample of 1039 persons from Framingham, Massachusetts, USA. This cohort is not to be mixed up with the Framingham Heart Study or the Framingham Offspring Study cohorts.

This is a cross sectional cohort. The subjects were aged 50-90 years at enrolment and were drawn from census tract data and random-digit telephone dialling. They were ambulatory and the selection was not made on the basis of knee or other joint problems and possible participants were unaware that knees were a focus of the study. Exclusion criteria were bilateral total knee replacement, rheumatoid arthritis, dementia, terminal cancer and contraindications to MRI.

Participants underwent weight bearing posteroanterior knee radiography with the fixed-flexion protocol[104]. One musculoskeletal radiologist, who was blinded to the MRI findings and clinical data, graded radiographs using the KL grading system. The KL grading system is commonly used for assessing the severity of osteoarthritic disease in the knee joint radiographically. We considered knees with KL=0 as free of radiographic OA and KL≥2 as having radiographic tibiofemoral OA.

The participants underwent MRI was with a 1.5 Tesla scanner and the scans were read by two expert musculoskeletal radiologists (who did not read the radiographs) using the Whole Organ MR Score (WORMS).

The study persons weight and height were measured. Body mass index (BMI) was divided in the categories: BMI (<25, ≥25-<30, ≥30). All participants were asked about knee pain in the last month. Descriptive statistics of the Framingham cohort used in Paper II-IV are presented in table 4.

Table 4: Descriptive statistics of the Framingham cohort used in Paper II-IV.

Characteristic	N=1003
Women, n (%)	565 (57)
Age, mean (SD) *years*	62.3 (8.6)
Body mass index, mean (SD) *kg/m²*	28.5 (5.6)
Kellgren and Lawrence grade, n (%) right knee	
0	749 (77.8)
1	43 (4.5)
2	90 (9.3)
3	54 (5.6)
4	27 (2.8)
Kellgren and Lawrence grade, n (%) left knee	
0	769 (80.1)
1	44 4.6)
2	73 (7.6)
3	49 (5.1)
4	25 (2.6)

12 subjects missing value for sex, 12 subjects missing value for age, 25 subjects missing value for BMI, 40 subjects missing value for KL grade right.

All subjects were asked about knee symptoms: ″In the past month, have you had any pain, aching or stiffness in your knee?″ Additional questions regarding knee pain were: ″Did you have knee pain lasting at least a month in the past year?″ and “Did you have knee pain on most days in the past month?″ Each participant was also filled out the Western Ontario McMaster University arthritis index (WOMAC) questionnaire. In Paper IV, where the association between meniscal extrusion and knee pain was investigated we used “knee pain some days last month” as a more sensitive and “knee pain most days last month” as a more specific question. Pain, aching and stiffness could be seen as symptoms for knee OA, but at the same time they can derive from other intraarticular alterations such as a meniscal tear. If they represent symptoms from an extruded meniscus was investigated in paper IV.

MRI readings

The main focus in this work has been on extrusion of the meniscus. Since the meniscus is a semi rounded structure, extrusion could occur in different directions. Due to the rigid attachment of the meniscal horns, the most extrusion occurs in medial and lateral direction and thereby on MRI it is best seen on the coronal view. The Boston Leeds Osteoarthritis Knee Score (BLOKS) and MRI Osteoarthritis Knee Score (MOAKS) use a four-item ordered categorical scale (0: < 2, 1: 2 - 2.9 mm, 2: 3 - 4.9 mm, 3: >5 mm extruded). WORMS initially did not define meniscal extrusion, but then a simple 3-item ordered categorical was added (0: absent, 1: ≤ 50% extruded, 2: >50% extruded)[98 102 103 105]. In the present studies however I used a quantitative measure in mm. This to give a precise measurement, which can be compared with other studies. Thus, in all four papers we used the method described by Hunter et al.[55]. The measurements were determined on the mid-coronal slice, where the medial tibia spine appeared largest. When it was too difficult to distinguish the maximal spine area between two or more slices, the slice with the largest tibia width was used. The point of reference for extrusion was the tibia plateau osteochondral junction at the joint margin excluding osteophytes. For the measurements a reference line was drawn between the medial and lateral osteochondral junction, defined as the tibia width (TW). Then parallel to the TW the medial meniscal coronal extrusion (MMCEx), lateral meniscal coronal extrusion (LMCEx), medial meniscal coronal width (MMCW), lateral meniscal coronal width (LMCW), medial tibia plateau width (MTPW) and lateral tibia plateau width (LTPW) were measured. (Figure 3). For extrusion readings we used the Merge eFilm software 3.4 and made all the measurement to the closest mm. In Paper I Katharina Bruns was trained by me and performed the extrusion readings. In Paper III-IV the readings were performed by me.

In both the OAI sample and the Framingham Community sample (i.e. for all four papers of the thesis) Martin Englund performed MR readings for meniscal integrity, i.e. tears or destruction in the anterior horn, body, or posterior horn. He regarded an increased meniscal signal as indicative of a meniscal tear when it communicated with the inferior, superior, or free edge of the meniscal surface (or more than one of those) on at least two consecutive images (or for a radial tear, if it was visible on both the coronal and sagittal images).

All other MRI readings in Paper II-IV were read according to WORMS, which is a scoring-method for multi-feature, whole-organ evaluation of knee OA. It has in many studies shown a high inter-reader agreement among skilled readers. This method has often been used in epidemiological studies. The knee is divided in 15 different regions segmented by anatomical landmarks. Each knee specific feature is graded separately within the region. Features considered in our study were cartilage damage, meniscal damage and BML.

Cartilage damage is considered present if there is a small focal loss less than 1 cm in greatest width or areas of diffuse partial or full thickness loss (WORMS grade ≥2).

Meniscal lesions (WORMS grade ≥1) included displaced or non-displaced meniscal tears or sign of previous surgery (including repair and partial or complete resection) and complete maceration or destruction within the anterior and posterior horns and the meniscal body.

BML, or marrow oedema, was considered existing if there are non-cystic subchondral areas of ill-defined high signal on proton density weighted MR images with fat signal suppression (WORMS grade ≥1).

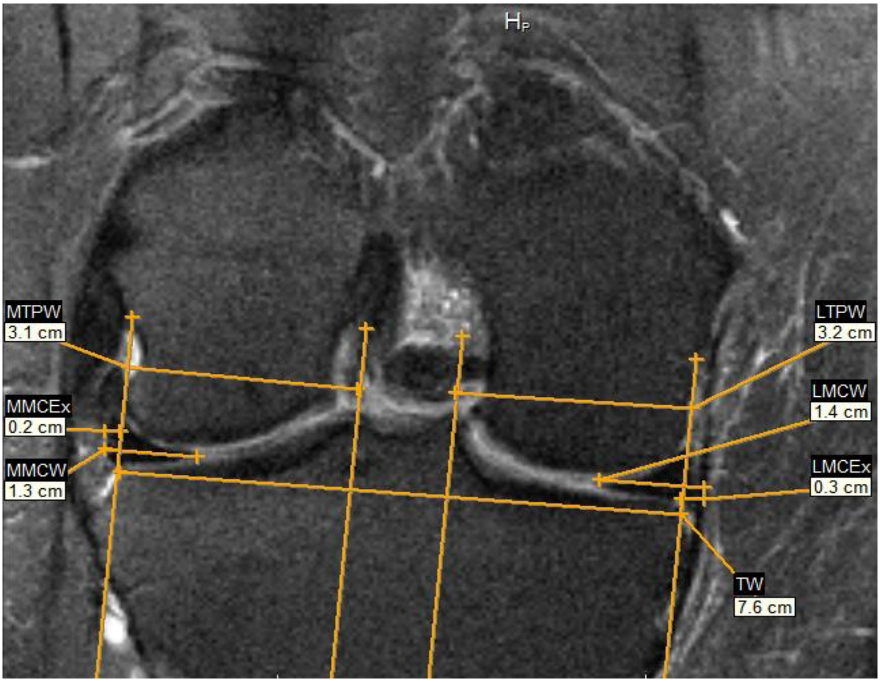

Figure 3 Method for measurements on MRI in all four papers.
TW = Tibia width, MTPW = Medial Tibia Plateau Width, LTPW = Lateral tibia Plateau Width, MMCW = Medial Meniscal Coronary Width, LMCW = Lateral Meniscal Coronary Width, MMCEx = Medial Meniscal Coronary Extrusion, LMCEx = Lateral Meniscal Coronary Extrusion.

Statistical analysis

In all papers we present descriptive data such as mean age, distribution between the sexes and BMI.

In paper I fifty randomly picked knees were re-measured and the intra-observer reliability (intra-class correlation coefficient, ICC) for Katharina Bruns was calculated. In paper I-III we assessed both the intra- (reader Fredrik Svensson) and inter-observer reliability (readers Fredrik Svensson and Fan Zhang) for all MRI measurements.

Since both meniscal width, meniscal extrusion, tibia width and bilateral tibia plateau width was measured we could performed a variety of calculated measurements for meniscal position and coverage in Paper I and II:

- Meniscal body extrusion ratio/index: (meniscus body extrusion)/ (tibia plateau width)
- Meniscal body extrusion ratio/index (ipsilateral): (meniscus body extrusion)/ (ipsilateral tibia plateau width)
- Meniscal coverage: (meniscus body width) – (meniscus body extrusion)
- Proportion (%) of the width of the ipsilateral tibia plateau covered by meniscus: (meniscus body width - meniscus body extrusion)/ (ipsilateral tibia plateau width)
- Proportion (%) of the width of the tibia plateau covered by the medial or lateral meniscus: (meniscus body width - meniscus body extrusion)/ (tibia plateau width)
- Overlap distance: (meniscal coronal width) – (meniscal body extrusion)

In Paper III and IV we choose not to apply any of these calculated measurements. Instead we only used medial meniscal extrusion in mm as measured on MRI. The reason in paper III was that we wanted to scrutinize just the commonly accepted 3 mm cut off for pathologic meniscal extrusion. In paper IV the underlying idea was that a bulging meniscus causes pain through its pressure against the joint capsule, making the relative measurements less interesting.

In Paper I the results were stratified by meniscal tear, i.e. subjects with and without tear at the baseline exam. We used a 2-level linear mixed regression model with a patient as a random effect to control for the correlation of measurements made in the same patient with adjustment for age and sex. The follow up time in Paper I was four years and any possible changes in meniscal body extrusion, overlap distance, or meniscal body coverage over time were analysed using a linear 3-level mixed effects regression model to account for correlation between measurements in the same person and knee. We used time as only fixed effect (using number of days between MR images obtained). We considered a two-tailed p-value of 0.05 or less as statistically significant.

In Paper II I calculated the distribution of both medial and lateral meniscal body extrusion stratified by sex. I also evaluated the meniscal coverage, both the absolute measure in mm, but also the proportion (%) of the width of the ipsilateral tibial plateau covered by meniscus. Early in the work we found that the proportion (%) of the width of the *whole* tibial plateau covered by meniscus was easier to perform. Also the size of the tibia width correlated well to the size of the medial/ lateral plateau. This calculated relative measurement was however discarded since using the ipsilateral tibial plateau (same compartment as the measured meniscus) was considered as more “true” In a multivariable linear regression model with robust standard errors, we estimated the association of age (continuous), BMI (continuous) and meniscus damage (yes/no) with medial and lateral meniscal body extrusion and coverage, stratified by sex, adjusting for the tibia width to take the size of the knees into account.

In Paper III, evaluated the most optimal cut-off for *pathological* meniscal extrusion with the aim to predict OA features in the knee. We constructed separate receiver operating characteristic (ROC) curves for each outcome; radiographic OA, BML and cartilage damage. In a ROC-curve (see Figure XXX as example) the area under the curve is measured and is ranged between 0.5 and 1.0. A straight line, or area 0.5, represents an insignificant test, while an area of 1 represents a perfect test. The area measures discrimination and was calculated using the medial meniscal extrusion in mm as predictor variable. The performance of the 3 mm “gold standard“ cut-off was evaluated by calculating sensitivity, specificity, positive and negative predictive value. We estimated a new cut-off that maximized the Youden index, which combines sensitivity and specificity into a single measure (Sensitivity + Specificity – 1)[106]. It is the point on the ROC curve which is farthest from line of equality (straight line, area 0.5) in order to maximize the correct classification rate. I also provided the percentage correctly classified subjects (also known as accuracy) for both cut-offs.

In Paper IV I evaluated meniscal body extrusion and its association with knee pain. For this task we constructed three different models with different amounts of potential confounders. In model 1 age, sex, BMI and meniscal tear were considered as confounders. In model 2 we added BMLs and cartilage damage as potential confounders. In model 3 we added prior knee injury “inability to walk for at least 3 days” and “requiring the use of crutches/cane” to model 2 as further potential confounders. Knee injury was considered as present if either of the two injury-statements was affirmative. All three models were put in a logistic regression, with logistic regression with “any knee pain” and “frequent knee pain” dependent variables and medial meniscal extrusion (MME) as the exposure of interest. We estimated the Odds ratio having pain when MME is 1 mm larger. We also estimated the risk ratio and relative risk. For easier understanding we renamed them prevalence ratio and prevalence difference. In the manuscript I choose not to present data for risk ratio (prevalence ratio). This, because it makes the manuscript easier to digest, especially for readers without sophisticated statistical knowledge. As an additional sensitivity analysis, in order to exclude intra personal confounders, we constructed a model with matched knees, where only one knee had “any knee pain” or “frequent knee pain”. For this analysis we used a fixed-effects logistic regression model, again with MME as exposure. This model was additionally also adjusted for knee injury as above.

For the statistical analysis we used R (Paper III), SPSS 19 (Paper I), SPSS 22 (Paper IV), Stata 12 (Paper I), Stata 13 (Paper II), Stata 14 (Paper III) and Stata 15.1 (Paper IV)[107 108].

Results

Paper I

The first paper, based on the OAI cohort, delivers an array of baseline data, for both the medial and lateral meniscus. Meniscal width, meniscal extrusion, extrusion index, extrusion index (ipsilateral), overlap distance and coverage are presented. Please see page 35 for definitions. These data are also stratified by meniscal damage. At the four-year follow up only meniscal extrusion, overlap distance and coverage were presented. The mean (SD) meniscal extrusion (right and left) was medially 1.64 (0.92) mm and laterally 0.63 (0.73) mm. Mean (SD) meniscal extrusion in knees with meniscal tear was medially 2.0 (0.87) mm and laterally 0.89 (0.93) mm. Medially women had a mean (SD) extrusion index of 2.4 (1.2) and men of 2.0 (1.4). Laterally the mean (SD) ratios were very similar: 0.8 (1.0) vs. 0.9 (1.0), but only the results medially had a significant p-value of p = 0.03. Extrusion index (ipsilateral) had no significant p-values. The main results as baseline and at the four-year follow up are presented in table 5.

Table 5: Results at baseline and change four year follow up (SD), Paper I. Right = right knee, Left = left knee.

	Measurements at baseline				Change at four year follow up			
Ipsilateral meniscal tear?	No		Yes		No		Yes	
	Right	Left	Right	Left	Right	Left	Right	Left
Medial meniscus:	N=109	N=110	N=9	N=8	N=101	N=94	N=8	N=7
Extrusion, mm	1.85 (1.04)	1.38 (0.73)	1.89 (0.78)	2.13 (0.99)	+0.27 (0.76)	+0.06 (0.60)	+0.25 (0.89)	-0.14 (1.22)
Overlap distance, mm	10.18 (3.60)	10.26 (3.52)	9.11 (3.14)	8.88 (3.31)	-0.20 (2.36)	+0.26 (1.98)	-0.25 (2.49)	-0.43 (1.99)
Coverage, %	34.7 (12.2)	34.9 (11.8)	29.2 (9.7)	28.7 (10.7)	-0.5 (8.0)	+0.7 (7.0)	-1.0 (8.2)	-1.4 (6.3)
Lateral meniscus:	N=112	N=115	N=6	N=3	N=103	N=98	N=6	N=3
Extrusion, mm	0.62 (0.77)	0.61 (0.67)	1.00 (1.10)	0.67 (0.58)	0.00 (0.54)	+0.12 (0.75)	+0.17 (1.17)	+0.33 (0.58)
Overlap distance, mm	9.90 (2.35)	9.78 (2.47)	8.00 (1.41)	7.00 (2.65)	+0.23 (1.46)	+0.26 (1.96)	+0.50 (0.84)	-0.33 (1.53)
Coverage, %	31.6 (7.4)	31.0 (7.8)	26.2 (7.6)	23.3 (7.8)	+0.7 (4.8)	+0.7 (6.1)	+1.6 (3.3)	-1.5 (4.0)

Medial meniscal extrusion had a tendency to increase over time, with an annually increase of 0.040 mm (95% CI: 0.019 – 0.062). The result was statistically significant, in both women and men, when stratifying the analysis by sex (data not shown). Laterally we found no statistically significant tendency for change of meniscal extrusion over time.

Paper II

In paper II, using the Framingham cohort, we determined meniscal extrusion and cartilage coverage and factors associated with these parameters in people free of radiographic OA. Initially we included all KL grades, but since we considered OA as a strong risk factor for meniscal extrusion we decided to only include knees with KL grade 0. In the article MME (SD) was 2.6 (1.2) mm in the right knee and 2.8 (1.1) mm in the left knee (both sexes combined). Here I present both knees with and without OA, which shows that OA seems to be strongly associated with meniscal extrusion. (Table 6)

Table 6: Distribution of meniscal extrusion (SD). N = number of persons

	All knees				Knees free of OA (KL = 0)			
	Right knee N=957		Left knee N=886		Right knee N=781		Left knee N=707	
Sex	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral
Men	3.0 (1.7)	2.1 (1.2)	3.1 (1.6)	1.6 (1.2)	2.7 (1.3)	2.1 (1.2)	2.9 (1.2)	1.6 (1.2)
Women	2.9 (1.7)	1.9 (1.4)	3.0 (1.4)	1.6 (1.2)	2.5 (1.1)	1.9 (1.2)	2.7 (1.1)	1.5 (1.0)

At large we found MME to be greater in older age, in knees with radiographic OA, which is illustrated in figure 4 and 5. Meniscal extrusion was also greater in knees with meniscal damage. On the other hand was BMI only associated with medial meniscus extrusion in women.

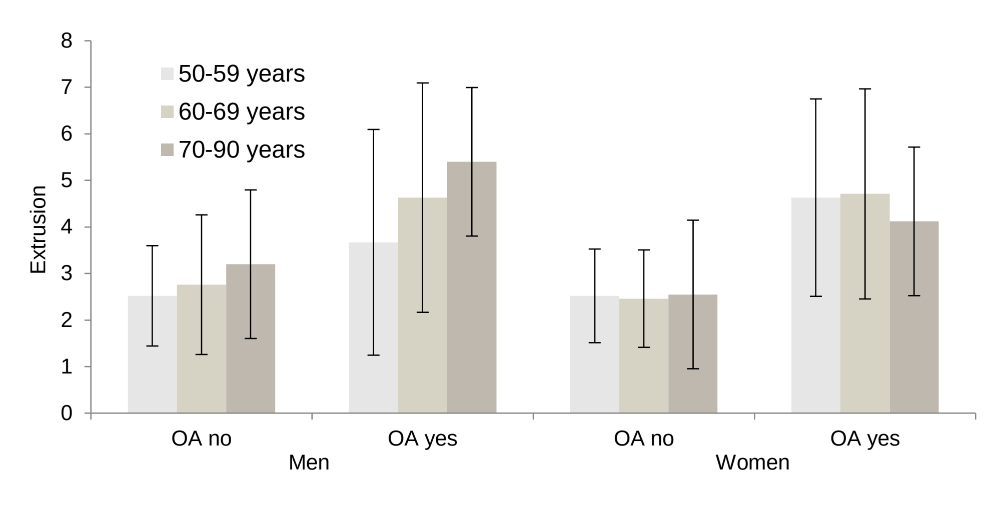

Figure 4: Medial meniscal extrusion stratified by age, OA-status and sex. Error bars showing standard deviation (SD).

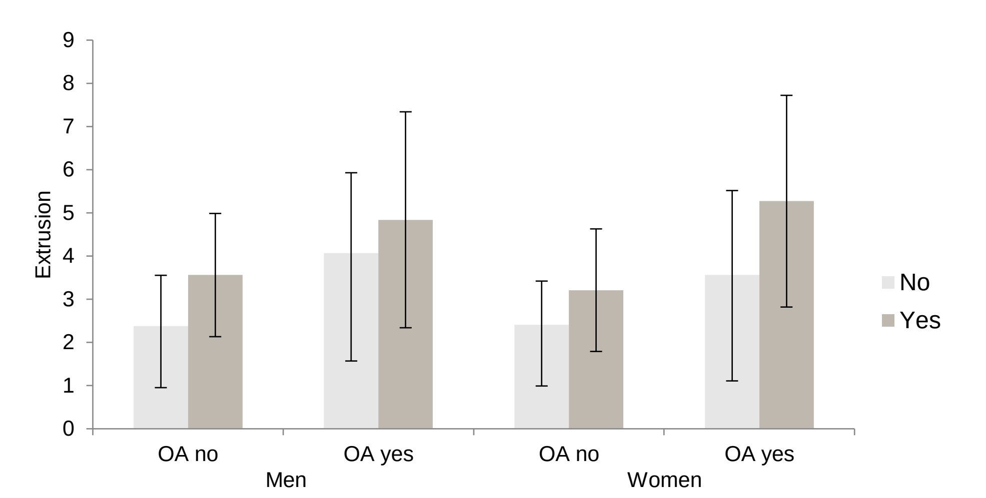

Figure 5: Medial meniscal extrusion in the right knee for both sexes stratified by meniscal damage and OA-status. Error bars showing standard deviation (SD). No = no meniscal damage, Yes = meniscal damage.

Mean meniscal coverage had different distributions between the medial and lateral compartments, also between right and left knees. As above, knees with OA had "inferior" values of coverage (table 7).

Table 7: Mean meniscal coverage (SD) in all knees and knees free of radiographic OA (KL grade 0). N = number of persons

	All knees				Knees free of OA (KL = 0)			
	Right knee N=957		Left knee N=886		Right knee N=781		Left knee N=707	
	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral
Men	7.3 (3.5)	10.0 (3.0)	9.3 (4.2)	10.0 (2.7)	7.8 (3.2)	9.9 (2.9)	9.9 (4.0)	10.0 (2.7)
Women	6.2 (3.0)	8.7 (3.0)	8.0 (3.7)	8.8 (2.6)	6.9 (2.5)	8.5 (2.9)	8.4 (3.4)	8.8 (2.5)

The multivariable linear regression analyses were made for the medial and lateral compartment, in men and women, respectively, with medial meniscal extrusion as exposure. For the medial compartment, we found statistically significant associations with higher age (men only), and meniscal damage. In the lateral compartment we found no statistically significant associations. Not reported in the article was that radiographic knee OA (KL grade ≥2) medially also had statistically significant associations in both sexes.

Paper III

In paper III we analysed the behaviour 3 mm as cut-off for "pathological" medial meniscal extrusion and estimated a new optimal cut-off for meniscal extrusion with respect to three structural features of OA; radiographic knee OA, bone marrow lesions (BMLs) and cartilage damage. Knees with one of the three features had overall larger medial meniscal extrusion. For example knees without radiographic OA had a mean (SD) medial meniscal extrusion of 2.6 (1.2) mm and those with radiographic OA 4.5 (2.3). Radiographic OA had the largest area under the curve (AUC) (Table 8).

Table 8: Area (AUC) under the receiver operating characteristic curve (ROC) for continuous meniscal extrusion as a predictor of 3 structural outcomes. N = number of persons, (95 % confidence interval).

Results from ROC-curves		
OA structural feature	N	AUC
Radiographic OA	936	0.76 (0.71-0.81)
BML	953	0.67 (0.63-0.71)
Cartilage damage	951	0.66 (0.62-0.69)

We reported the performance of the 3mm as well as the new estimated 4mm cut-off, which maximizes the Youden index[106]. The actual derived optimal cut-off was 3.5mm, but since meniscal measurements only were performed to the closest mm we had to round up to 4mm. Sensitivity, specificity, positive predictive values, negative predictive values and accuracy (% correctly classified objects) were calculated (Table 9).

Table 9: Discriminatory accuracy of extrusion cut-offs. Numbers are estimates as % with 95% confidence intervals in parentheses. Radiographic osteoarthritis (OA) = Kellgren and Lawrence (KL) grade ≥2, bone marrow lesions (BML) = WORMS grade ≥1, Cartilage damage = WORMS grade ≥2.

	OA structural feature	
	Radiographic OA	
Cut-off	3 mm	4 mm
Sensitivity	81 (73 - 87)	63 (60 - 65)
Specificity	49 (45 - 52)	82 (81 - 83)
Positive predictive value	24 (20 - 27)	41 (40 - 43)
Negative predictive value	93 (90 - 95)	92 (91 - 92)
% correctly classified	54 (51 – 57)	79 (78 - 80)
	BML	
Cut-off	3 mm	4 mm
Sensitivity	74 (68 - 79)	46 (43 - 48)
Specificity	51 (47 - 55)	79 (77 - 81)
Positive predictive value	37 (33 - 41)	48 (46 - 50)
Negative predictive value	83 (79 - 87)	79 (78 - 79)
% correctly classified	57 (54-61)	70 (68 - 71)
	Cartilage damage	
Cut-off	3 mm	4 mm
Sensitivity	68 (63 - 73)	39 (37 - 41)
Specificity	54 (49 - 58)	84 (82 - 85)
Positive predictive value	54 (50 - 59)	67 (65 - 69)
Negative predictive value	67 (63 - 72)	63 (62 - 64)
% correctly classified	60 (57 – 63)	64 (63 - 65)

Paper IV

In this paper we investigated the association between medial meniscal extrusion and pain in knees free of radiographic OA (KL grade 0). Mean (SD) MME for all right knees was 2.6 mm (1.2), in knees with no knee pain 2.3 (1.14) (Table 10).

Table 10: Mean MME and meniscal tear in the right knee stratified by pain status.

	All cases	No pain	Any pain	Frequent pain
N	407	301	78	55
MME (SD)	2.4 (1.1)	2.3 (1.1)	2.8 (1.0)	2.8 (1.1)
Meniscal tear (%)	57 (14)	41 (13.6)	12 (15.4)	10 (18.2)

As described above we reported logistic regression with two knee pain parameters (binary) as outcome and meniscal extrusion as exposure. In the article we reported Odds ratio and risk difference (prevalence difference) in model 1-3. Risk ratio (prevalence ratio) was omitted, due to easier reading of the manuscript, but is here reported. The odds ratio is different from the risk ratio, although the odds ratio approximates the risk ratio when the outcome is rare (typically below 10%) (Table 11).

Table 11: Association between any and frequent knee pain and medial meniscal extrusion. OR= odds ratio, PR = Prevalence ratio, PD = prevalence difference, (95% confidence interval).

	Any knee pain			Frequent knee pain		
	OR	PR	PD	OR	PR	PD
Model 1 (adjusted for age, sex, BMI, meniscal tear)	1.19 (1.01, 1.40)	1.16 (1.00, 1.34)	2.3% (0.7, 3.9%)	1.09 (0.91, 1.31)	1.08 (0.92, 1.26)	1.0% (-0.8, 2.8%)
Model 2 (Model 1+BML, cartilage damage)	1.17 (0.99, 1.38)	1.14 (0.98, 1.31)	2.1 % (0.4, 3.9%)	1.06 (0.88, 1.27)	1.05 (0.90, 1.22)	0.7% (-1.4, 2.6%)
Model 3 (Model 1+2+Injury, inability walk 3 days and using a crutch)	1.15 (0.97, 1.37)	1.12 (0.97, 1.28)	1.9 % (0.0, 3.7%)	1.04 (0.86, 1.26)	1.03 (0.89, 1.21)	0.5 % (-1.6, 2.6%)

In the sensitivity analysis, where we used *both* knees from subjects discordant for any or frequent knee pain, respectively, in a matched design the odds ratio (95% CI) per 1 mm greater MME was 1.35 (0.95, 1.91) for any knee pain. (Table 12).

Table 12: Results from analysis with matched knees discordant for knee pain.

	Any knee pain		Frequent knee pain	
	Odds ratio	95% CI	Odds ratio	95% CI
Adjusted for knee side only	1.35	(0.95, 1.91)	1.50	(0.93, 2.42)
Additionally adjusted for knee injury	1.47	(0.94, 2.31)	1.61	(0.92, 2.85)

Discussion

What is normal meniscus position? When is it no longer normal? Can it be painful?

These questions formed the backbone of my thesis. There cannot be a short and definite answer, but all in all I want to state that we have provided novel and important information.

Meniscal extrusion is often used as a proxy for meniscal position. Unquestionably this is a simplification. Since no knee has the same shape or size as another, more information is necessary to provide an accurate measurement.

In this work I used the well described two-dimensional measurement on coronary MRI[54]. This is a quite simple method for measuring meniscal extrusion. Of course would a technique with full 3D segmentation including the roots of the meniscus and its position deliver more information. For instance Eckstein et al have some well written publications with meniscus segmentation[57 109-111]. A full segmentation technique is quite time consuming, hence unsuitable in larger sample sizes[58 112-114].

In paper I and II we also suggested dividing the meniscal extrusion by the whole tibia width or ipsilateral tibia plateau width as a relative measurement. Relative measurements are well suited for describing data, but lack the accuracy when analysing the connection between risk factors and extrusion[115]. Since between 40% and 70% of total axial load in the knee joint has been reported to be transmitted by the menisci; the rest through direct contact of articular cartilage, we also provided coverage and relative coverage to take this into account[116]. Meniscal overlap is supposed to represent how much of the whole meniscus is actually directly involved in load distribution.

“Normal” meniscus position

MME of 3 mm is often seen as “gold standard”. In 1999 Gale et al found a MME (SD) of 2.9 mm (2.2) in men and 2.7mm (2.1) in women[51]. These subjects had no knee pain, but no distinction was made for joint space narrowing (JSN). Costa et al determined that MME of 3 mm is associated with extent of meniscal degeneration and tear[43]. These findings were corroborated by Leerer et al. They concluded that

MME ≥3 mm is strongly associated with degenerative joint decease, meniscal root pathology and radial tear[117]. In the literature, there is still considerable lack of information on meniscal positioning from persons without radiographic knee OA.

In paper I mean MME was only 1.6 (0.9) at baseline. In paper II MME (SD) in the right knee was 2.6 (1.2) mm and 2.8 (1.1) mm in the left knee. The population in paper II is more representative for a "normal" population; while paper I is based on the "non-exposed" OAI cohort, which makes it difficult to compare them to other studies. Wenger et al also used OAI data but a cohort *with* knee OA and found a MME (SD) of 2.6 (1.1) mm[57].

The lateral meniscus has in the literature not been given the same interest. Gale et al found lateral extrusion to be 0.4 (1.4) mm in men and 0 (0) mm in women. Wenger et al reported a lateral meniscal extrusion (SD) of 1.16 (0.48) mm in knees with OA. In paper I we found a lateral meniscal extrusion (SD) of 0.63 (0.73) mm at baseline. In paper II the corresponding values (SD) were 2.0 (1.2) mm in the right knee and 1.5 (1.1) mm in the left knee.

Meniscal damage and extrusion are two frequently cited risk factors for knee OA[43 45-51 54-58 60 61 63 66 118-120]. What comes first, extrusion or damage, is not always certain, but it's important to keep in mind that meniscal extrusion is a combined construct of radial displacement, potential intrameniscal change and reduced hoop-strength, which alters the width. Many authors regard meniscal extrusion and damage to be on the pathway to knee OA. In both the OAI and Framingham cohort it was obvious, that knees with meniscal damage/tear overall had larger MME. The cohort size in Paper I was only 122 subjects and the sample sizes with meniscal tear were very small, whereby limiting our ability to make any conclusions with respect to tears. The Framingham cohort was larger and we found statistically significant associations of MME with ipsilateral meniscal damage. Neither of the two papers could however show a statistically significant association between lateral meniscal extrusion and meniscal tear/damage. My own hypothesis, is that since the lateral meniscus has a more "loose" anatomical fixation, its position doesn't change as much when being damaged. Also the lateral meniscus transmits a smaller part of the axial load. One should also not forget that the shape and size of the meniscus can influence the amount of extrusion[121 122].

Overall, in Paper I, were the results for extrusion index, extrusion index (ipsilateral), meniscal overlap and coverage "worse" in knees with meniscal damage/tear. Again are the sample sizes in paper I very small. Meniscal coverage is reported in paper I and II and again with "worse" covering when the meniscus is teared/damaged. In paper II we had no statistically significant associations at all in the lateral compartment. This could probably again reflect the theory that the medial and lateral meniscus play by different rules. Our finding of more medial meniscal extrusion in knees with medial meniscal tear/damage is in agreement with previous reports[43 47 66 123].

Does meniscal extrusion change over time and is it larger in higher age? There is a paucity in the literature regarding meniscal positioning over time. In Paper I we found proof for small changes of MME but not for lateral meniscal extrusion over four years. Interestingly did meniscal overlap and coverage not show any essential changes. This could lead to the suspicion, that the change over time, at least to some extent, is the result of degenerative flattening of the meniscus. Bloecker et al used an OAI cohort with JSN and a 3D segmentation of the meniscus. They reported a decrease in medial and lateral coverage over two years and observed that the reduction in coverage medially was due to an increase in MME and decrease in width, while laterally, there was a reduction in meniscus width, but no change in extrusion[109]. As in our OAI-study, the changes over time were very small. Physiological degradation of meniscal tissue and its displacement is most likely a slow process. The change over time is probably not a linear progression and could accelerate in the case of meniscal damage or enhanced OA progress. In this context, two or four years is a short time of observation. In paper II we did stratify the results by age, but since it is a cross-sectional study no longitudinal conclusions are possible. In paper II MME was larger in higher ages, but MME and medial coverage only had a statistical significant association with age in men. Again, meniscal extrusion is associated to meniscal damage and there was an association between MME and coverage with meniscal damage.

Other reflections from paper II are that women had similar degree of meniscal body extrusion and cartilage coverage as men and the overall impact of BMI on meniscal extrusion in this cohort was low. The possible impact of obesity (i.e. high BMI) on meniscal extrusion probably plays a greater role in MRI *with* loadbearing.

"Pathological" meniscal extrusion

When defining pathological meniscal extrusion, choosing a proper definition is crucial. The 3 mm threshold to denote pathological MME is frequently used for both research purposes and to some extent in clinical situations. It was our opinion, that this cut-off not has been satisfactorily scrutinized against structural knee pathologies and there is lack of evidence of what may be regarded as "pathologic". Not all pathologies detected on knee MRI give any symptoms, so it's important to separate radiographic and clinical findings in each patient[60]. In paper III and IV we separated radiographic pathologies from pain and we choose to assess only the medial compartment, while we appreciated the lateral compartment more seldom to be involved in osteoarthritic changes. In our evaluation of the primary results in paper

III it became obvious, that a clear cut border for pathological meniscal extrusion cannot be stated. Each cut-off results in compromising either sensitivity or specificity. We found the best compromise to be 3.5 mm (rounded up to 4mm due to inaccuracy of the Efilm software).

The 3 mm cut-off for MME had high sensitivity, but quite low specificity as a marker of the three used structural OA features. The main difference between the results for cut-off 3 mm and 4 mm is a shift towards higher percentage correctly classified subjects (i.e. accuracy) and a shift from high sensitivity and low specificity to lower sensitivity and high specificity. The higher percentage correctly classified subjects of this approach come partly from the fact, that in the whole cohort there are more persons *not* having the outcome than having the outcome.

Of course there is a "trade-off" from high sensitivity to higher specificity. We assumed that the cost of sensitivity and specificity is the same (i.e. it is equally "bad" to classify a person without outcome as having the outcome and to classify a person not having an outcome as having an outcome). This is important, not only for study purposes. Since the 4 mm cut-off has a lower false positive rate we emphasize its importance in a clinical setting.

There is still limited knowledge in the importance of meniscal extrusion for pain in knees free of OA[51]. In the knee joint, tissues containing nociceptors include primarily the joint capsule, ligaments, synovium, bone, and the outer edge of the menisci. Nociceptive stimuli are likely to originate from one or more of these locations in people with knee pain[124]. With so many co-occurring structural features in knees with radiographic OA, it's difficult to tease potential effects one from another. In addition the perception of pain is modulated by age, mental status, cultural background etc. In this context we found it of interest to explore how likely it is for MME to be associated with knee pain in subjects free of radiographic OA. We used two self-reported definitions for knee pain, this since "any knee pain" could be considered a more sensitive outcome but more unspecific, and a question on "frequent knee pain" could be considered less sensitive but more specific.

In paper IV the odds ratios and 95% CI for pain per 1 mm greater MME were all rather consistent suggesting a possible weak association between MME and knee pain. However, the estimates of association are typically included in the 95% confidence interval. The matched within-person analysis which adjusts for person-level confounding confirmed our primary analysis. Our findings are similar to those reported by Wenger et al where MME $\geq$3 mm was more frequent in painful than in painless knees[57].

To detect and choose the right confounders is crucial for the results in paper IV. Age, sex, BMI and meniscal tear are in our opinion confounders for knee pain. The role of BML, cartilage damage and previous knee injury are not as clear and were therefore used in a separate model (model 2 and 3). The secondary analysis with matched knees excluded all confounders on a personal level, but not the knee-specific ones such as meniscal tear. All the mentioned confounders are mostly more common in knees with OA[47 48 52 54 55 60 125-131]. Therefore we choose only to include knees with KL-grade = 0. Of course there are different ways of evaluating OA radiographically, but plain x-rays graded according to Kellgren and Lawrence is the standard method for assessing progression of knee OA[55 98].

Since we define 4 mm MME to be the best cut-off for pathological extrusion one could question why we did not test that threshold and its relation to pain. The reason is that we had very few subjects with MME > 4 mm and even fewer with reported knee pain, so the sample size would be too small.

As mentioned before, this was a cross-sectional study. The 4 mm cut-off can only be a border for estimating the risk of simultaneously having radiographic OA, BML or cartilage damage. Any statement regarding development of future knee OA or knee pain can unfortunately not be made based on these data.

In conclusion do paper II and IV suggest that MME is strongly associated with OA, but its relation to pain in knees free of radiographic OA is questionable. It cannot be disregarded, but an extruded meniscus is unlikely to be the sole reason for knee pain

Conclusions and clinical implications

We found that the mean medial body extrusion in the general population of mainly Caucasian middle-aged and elderly persons without tibiofemoral OA is close to 3 mm, which corresponds to a commonly used cut-off in radiology to denote pathological extrusion. In knees without knee pain or eligibility risk factors for knee OA the meniscal extrusion is substantially smaller.

There was a small tendency to increased medial meniscal body extrusion over a 4-year period. However, most meniscal position parameters remained relatively stable.

For the medial compartment, factors associated with meniscus position were predominantly ipsilateral meniscus tear or maceration/ destruction. For the lateral compartment, no similar associations were found.

Medial meniscal body extrusion is strongly associated with OA. The cut-off value 4 mm may be a better cut-off to use than 3 mm as it maximizes the sensitivity and specificity with respect to radiographic OA, bone marrow lesions and cartilage damage. Thus, we suggest that medial meniscal body extrusion of 4 mm or more may be considered as an alternative cut-off to be used mainly for epidemiologic study purposes, when categorizing is necessary, but to some degree also in a clinical setting.

Medial meniscal body extrusion may have a weak association with knee pain in knees free of radiographic OA. However, even with an extruded meniscus in a painful knee, the cause of pain in is most likely a multi-factorial complex entity. For a clinical situation it's important to keep in mind that meniscal extrusion has a strong association with knee OA, which primarily is the most probable reason for knee pain.

The study persons used in my thesis were all middle aged or older. Therefore no clinical implications can be made for younger persons. This is important when deciding the best treatment for each patient. The treatment options in young and older patients can vary a lot. A young patient is less likely to have knee OA and for example could a meniscal root tear with a secondary extrusion be treated with arthroscopic meniscus suture. In an old patient with knee OA physiotherapy and/or knee arthroplasty would more likely be the suitable choice.

Future perspectives

It's my opinion, that this work has widened the knowledge of meniscus position and its associations with knee symptoms and knee OA. Still there are many questions that need to be answered.

What is the normal meniscus position in a younger population? In this work the meniscus position did not change much over four years, but does it change over a longer period? Is there a cut-off in time associated with OA, when the meniscus starts to "move"? What is the normal meniscus position in a knee with load bearing? When load bearing, are there any key features, such as meniscal root tear or knee OA, which predict a larger range in the meniscal extrusion?

These questions obviously need large longitudinal datasets with at least ten years of follow up. To my knowledge there is no such dataset or ongoing study. This would be a large scale project. Since the study persons at baseline would be "young" and probably without knee OA, they could be collected as patients in orthopaedic clinics. Then a healthy control group could be community based. At this moment we have no plans for such a study, but during the finishing work of my thesis it has woken my interest and will be discussed with my co-workers.

Such a large scale project may not be possible. Most patients seeking medical care for solely meniscal alterations are middle age or younger. This patient category is more prone to be treated with arthroscopic meniscus surgery. A somewhat smaller study could at least describe the normal meniscus position in the young (without knee OA), which would automatically have strong clinical implications.

Limitations of the studies

For all meniscal positions readings we used a relatively simple 2-dimensional measurement technique on the mid-coronal slice, a technique that does not provide as much detailed information as full 3D segmentation. The latter is though costly, time-consuming, requires special training and thus often not suitable in larger study samples.

Due to funding limitations and time constraints we included only the study of meniscal body position. The position of the anterior and posterior horn needs additional attention. This because foremost posterior root tears often lead to meniscal body extrusion.

The MRI reading software we used (Efilm 3.4) only allowed measurements to the closest millimetre. As we are dealing with small measurements such as meniscal extrusion, measurements to a tenth of a millimetre would have been preferable using alternate imaging software.

The knee MRIs were taken in standard non-weight-bearing and we cannot exclude the possibility of changes in meniscus position as compared to weight-bearing. However, currently, weight-bearing knee MRI is seldom available for epidemiologic studies or in a clinical setting.

The follow up period in paper I of four years is somewhat short in order to make any crucial assumptions. The dataset in the other three papers are cross sectional, where no future predictions, such as progression of OA, are allowed. In order to make any genuine individual conclusions longitudinal datasets, preferably with longer follow up period, is needed.

Small sample sizes, in paper I subjects with meniscal damage, few subjects with meniscal extrusion larger than 4mm, and perhaps there is a threshold needed, where the bulging effects on the joint capsule may cause knee pain.

However, pain is an utterly difficult construct to capture and quantify which represents a universal challenge in research. Examination with palpation of subjects' knees to determine medial joint line tenderness would have been an alternative and more precise outcome but was unfortunately not performed at the time of cohort examination

Populärvetenskaplig sammanfattning

Knäartros

Artros är en vanlig folksjukdom och knäleden är en av de mest drabbade lederna. Det är en vanlig orsak till smärta hos medelålders och äldre människor. Orsaken till artros är inte bara ”vanlig” förslitning, utan beror på flera olika orsaker. Några kända riskfaktorer för knäartros är övervikt, hög ålder, tidigare skador i anslutning till leden, kvinnligt kön, ledinflammation och kronisk överbelastning genom tungt arbete. De vanligaste symptomen är stelhet och smärta. Diagnosen knäartros ställs genom klinisk undersökning av knät och vid behov med hjälp av röntgenundersökning.

Meniskerna

Meniskerna som är två halvrunda broskskivor inuti knäleden har flera funktioner, men huvudsakligen så hjälper de till att fånga upp och jämna ut de belastande krafterna genom leden. Om meniskerna är skadade, så riskerar de tappa sin funktion och kan på så sätt bidra till utvecklingen av knäartros. Skador på meniskerna kan i sig vara smärtsamma, men ofta även helt utan symptom. I min avhandling har jag velat belysa vad som är meniskernas normala läge inne i leden och om detta har någon koppling till knäartros och smärta. Som ett mått på meniskens läge har vi använt menisk-extrusion, vilket är ett mått på hur stor del av menisken som ligger utanför ledytekanten. Extrusionen och även flera andra parametrar har mätts på MRT-bilder (magnetkamera). I tidigare forskning har man antagit att gränsen för ”normal” menisk-extrusion ligger vid ca 3 mm.

Material och metoder

Som material har vi använt oss av två databaser, där man sedan tidigare gjort både MRT och vanlig röntgen av knäleder hos friska försökspersoner. Man har samlat in en hel del andra data såsom ålder, kön, vikt, information om tidigare knäskador, knäsmärta etc. I den första artikeln använde vi oss av den amerikanska databasen Osteoarthritis Initiative (OAI). För vårt arbete valde vi en subgrupp som anses ha helt friska knän, dvs. försökspersonerna hade ingen känd knäartros, ingen knäsmärta och inga riskfaktorer för artros. De övriga tre delarbeten bygger på data från Framingham Osteoarthritis Study. Det är en databas, också från USA, men med slumpvist utvalda personer som är 50-90 år gamla. Tanken är att denna databas ska kunna representera en normalbefolkning.

På MRT-bilderna har jag (i delarbete 1 Katharina Bruns) mätt menisk-extrusionen på alla knän som haft tillräckligt bra bildkvalitet.

Resultat

I delarbete 1 mätte vi extrusionen hos båda meniskerna (på insidan och utsidan av knäleden). Det gjordes även mätningar efter en period på fyra år för att se om det blivit någon förändring. I genomsnitt var extrusionen 1,6 mm på insidan och 0,6 mm på utsidan av knät. Kvinnor hade en tendens till större inre extrusion i förhållande till knäts storlek. Förändringarna efter fyra år var minimala.

I delarbete 2 ville vi fastställa vad som är normal menisk-extrusion hos personer utan knäartros. Därför uteslöt vi alla personer som hade tecken till artos på vanlig röntgen. I genomsnitt var extrusionen 2,7 mm på insidan och 1,8 mm på utsidan. Både på in- och utsidan så var ca 30 % av knäledsbrosket täckt av menisk. Detta kan ses som ett mått på hur väl meniskerna fångar upp krafterna genom knäleden. Vidare fann vi att knän som hade en skada i ena menisken hade tydligt större extrusion.

Vad som kan anses vara sjuklig menisk-extrusion har inte undersökts tillräckligt noga. Därmed blev detta målet med delarbete 3. Eftersom den inre menisken oftare är skadad och sannolikt spelar större roll i utvecklingen av knäartros, så valda vi att bara fokusera på den. Vi undersökte om det fanns någon koppling mellan menisk-extrusion och knäartros (på vanlig röntgen), broskskada eller benmärgsödem. De två sistnämnda parametrarna är tecken till knäartros som kan ses på MRT. Dessutom beräknade vi den grad av menisk-extrusion, där det är mest sannolikt att man samtidigt har en av de tre nämnda parametrarna. Resultaten visade att det finns en koppling mellan menisk-extrusion och alla tre paratmetrar. De som hade artros på vanlig röntgen, broskskada eller benmärgsödem hade även större extrusion. Vi kom fram till att en menisk-extrusion på 4 mm var det mest känsliga och precisa måttet för att samtidigt ha tecken till artros på vanlig röntgen eller MRT.

I det sista delarbetet ville vi undersöka om bara menisk-extrusion i sig själv är smärtsamt. Ofta har man ju samtidigt både knäartros och en skada i menisken, vilket kan bidra till smärtan. Precis som i delarbete 2 så uteslöt vi alla försökspersoner med knäartros på vanlig röntgen. Alla fick svara på frågor angående om de haft smärta i knät den senaste månaden. I en s.k. regressionsanalys kunde vi sedan utesluta den potentiella smärteffekten av hög ålder, kön, vikt, skada i menisken, benmärgsödem, broskskada och tidigare knäskada. På så sätt försöker man filtrera ut risken för att det *bara* är menisk-extrusionen som gör ont. Resultaten visade att det bara finns en svag koppling mellan ”enbart” menisk-extrusion och knäsmärta.

Sammanfattning och konklusioner

Vi kom fram till att den genomsnittliga menisk-extrusionen på insidan av knäleden är ca 3 mm hos friska medelålders eller äldre individer. Om man samtidigt har artros eller någon skada på knät, så har man sannolikt större extrusion. Om man däremot har ett helt friskt knä utan känd risk för knäartros, så har man sannolikt mindre extrusion. Under en kortare period, som fyra år, ändras menisk-extrusionen inte väsentligt. Meniskextrusion på insidan av knäleden har en tydlig koppling till olika mått av knäartros på vanligt röntgen och MRT. 4 mm får anses vara det säkraste måttet på menisk-extrusion för att samtidigt ha knäartros. Enbart meniskextrusion gör sannolikt inte ont, utan knäsmärta är som både min och tidigare forskningar har visat en sammansatt effekt av olika faktorer.

Med detta arbete har vi kunnat belysa vad som är meniskernas normala läge inne i knäleden och kopplingen till menisk-skador, knäartros och smärta. Jag anser att detta arbete har gett ny och viktig information både för den kliniska vardagen och för framtida forskning.

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