Meniscus extrusion: risk factors & consequences

Meniscus extrusion: risk factors & consequences

Fan Zhang



DOCTORAL DISSERTATION

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| AbstractMeniscal extrusion is associated with meniscal tear, degeneration and even knee OA. MRI is an ideal tool to assess knee joints tissues and pathologies such as meniscal tears and extrusions. This thesis provides focus on the risk factors of meniscal extrusion as well its development and consequence, impact to other tissues and choices for clinical treatment.Patients free of radiographic knee OA (n=340) would have enlarged meniscal extrusion over a 72 months period. Female gender, incident meniscal tear, and higher baseline value of extrusion are shown to be risk factors for increased meniscal body extrusion. The results suggest that meniscal extrusion may contribute to and mediate the well-known increase in knee OA incidence in middle-aged women.Among overweight and obese women (n=395), ipsilateral meniscus tear and high BMI are factors associated with medial meniscus body extrusion based on my cross-section study of PROOF trial. Base on the same baseline meniscal extrusion data, analysis for 18 month incident/enlargement bone marrow lesions show meniscal body extrusion is an important factor influencing BML development, and thus a potential treatment target in early knee OA. The influence is more profound in the lateral knee compartment.Whether surgical or conservative method is more superior for treating meniscal pathologies is still in debate, investigation on meniscal body extrusion found APM in patients with OA does not differ significantly compared with the effect of non-operative management. |
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Fan Zhang



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## List of papers

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## Abbreviations

|  |  |
| --- | --- |
| 95% CI  | 95% confidence interval |
| ACL | Anterior cruciate ligament |
| APM | Arthroscopic partial meniscectomy |
| BMI | Body mass index |
| BML | Bone marrow lesion |
| ITT | Intention to treat |
| K-L | Kellgren-Lawrence |
| MOAKS | MR Imaging Osteoarthritis Knee Score  |
| MRI | Magnetic resonance imaging |
| NIH | National Institute of Health |
| OA | Osteoarthritis  |
| OAI | Osteoarthritis Initiative  |
| OR | Odds ratio |
| PCL | Posterior cruciate ligament |
| RCT | Randomized control trial |
| PROOF | Prevention of Knee Osteoarthritis in Overweight Females  |

# Introduction

## The meniscus

### Gross anatomy

The human menisci are two crescent-shaped [fibrocartilaginous](https://en.wikipedia.org/wiki/Cartilaginous%22%20%5Cl%20%22Fibrocartilage) discs located in the knee joint cavity between the surfaces of femur and tibia, on the medial and lateral side, respectively. The meniscal surface facing the tibia is flat and the surface facing femur is concave. This anatomy articulates the convex femoral condyles and the relatively flat tibial plateau effectively. The menisci are anchored to the underlying subcondral bone of tibial plateau by meniscal ligaments1, 2. At the anterior and posterior meniscal horns, circumferential matrix fibers continue as ligaments attached to the intercondylar bone.

The medial meniscus is C-shaped and covers up to 60% of the articular contact area of the medial tibial compartment3-5. Its posterior horn is much wider than the anterior horn. It is attached to the tibia by the anterior and posterior horns and the peripheral border merges with the knee joint capsule. And it is firmed attached to the medial collateral ligament.

The lateral meniscus is almost circular. Compared with the medial meniscus it is smaller and has more central attachments to the intercondylar area. And the lateral meniscus is separated from the lateral collateral ligament and the joint capsule at the popliteal hiatus. The structure makes the lateral meniscus more mobile than the medial meniscus.

The posterior horn of the lateral usually has attachments to the medial femoral condyle, occasionally to the posterior cruciate ligament (PCL)6. The ligament of Humphrey is anterior and the ligament of Wrisberg is posterior to the PCL.

In 44% to 58% of knee magnetic resonance images (MRIs), the transverse or anterior intermeniscal ligament is noted. Although it has variable attachments, for more than half (58%) cases this ligament runs between the anterior margin of the lateral meniscus and the anterior horn of the medial meniscus thus connecting the two anteri or horns7. (Figure 1)

### Vascular anatomy

The meniscus has limited peripheral blood supply. Branches from medial, lateral and middle geniculate arteries nourish each meniscus. The peripheral border of lateral meniscus is infiltrated by capillaries that penetrate 10-25% of the meniscus width. For the medial meniscus the corresponding figures are 10-30%. The anterior and posterior horns have rich blood supply by radial branches from a peri-meniscal plexus8. The vascularization structure of the meniscus is very important for healing9-11. A direct nourishment route is provided by the terminal loops which are formed with endoligamentous vessels from the anterior and posterior horns12. Other parts of the meniscus are nourished by synovial diffusion or mechanical motion.

### Neuroanatomy

The peripheral part of the meniscal tissue is innervated by the tibial nerve. The fibers typically follow the blood vessels and are primarily found in the peripheral vascular zone covering the outer third part of the meniscus13, 14. Three different mechanoreceptors have been identified in the meniscus. These neural elements are mostly concentrated in the meniscal horns especially the posterior horn. The meniscus horns are the richest innervated whereas the inner two thirds of the meniscus have no nerve innervation8, 15, 16.



Figure 1.

Head of right tibia seen from above, showing menisci and attachments of ligaments (Henry Gray: Anatomy of the Human Body 1918)

## **Biochemistry**

The meniscal matrix is a kind of dense extracellular matrix. Its constituents are mainly water (72%) and collagen (22%). Other components include proteoglycans, DNA, elastin and adhesion glycoproteins. The proportions of these components differ by age, trauma or pathologies17.

Collagen is distributed differently at different parts of the meniscus. The main function of collagen is to provide the meniscus with tensile strength. . Unlike articular cartilage, meniscal collagen is mainly of type I instead of type II. In the red zone, type I collagen composes 80% of the dry weight. The type I collagen fibres are mainly circumferentially oriented. In the white zone, collagen composes 70% of the dry weight. Of this collagen 60% is type 2 while 40% is type I18. The proteoglycan content is much lower in the meniscus than in articular cartilage19.

The classification of meniscal cells is still a topic of controversy20. Histological examinations have revealed that fibrochondrocytes or chondrocyte-like cells exist in the inner white zone of the menisci. Oval or fusiform shaped cells are found in the red zone. Flattened and fusiform cells which have no cell extensions are identified in the superficial zone of the meniscus and are supposed to be special progenitor cells capable of regeneration.

### Functions

The menisci have many significant biomechanical functions, which are determined by their structure, composition and morphology. The most prominent functions of the menisci are load transmission and shock absorption during dynamic knee joint movements 21-24. The knee meniscus increases the joint congruity and contact area and thus prevent focal concentration of stress25. The stress is thus distributed on a larger area of the articular cartilage. Other functions include joint stability, lubrication and proprioception 26-31.

## Knee Osteoarthritis

Osteoarthritis (OA) is one of the main reasons for disability all over the world, affecting one quarter of global population over 18 years-old32. With a steadily aging population and an increased prevalence of obesity, OA will have an increased impact on the patients’ daily work, normal activities and health care systems 33. Based on etiopathogenesis, OA was suggested to have four clinical phenotypes: biomechanical, osteoporotic, metabolic and inflammatory 34.

The knee is one of the most frequently affected joints by OA. Knee OA is characterized by progressive loss and breakdown of articular cartilage and thickening of the subchondral bone. Chronic pain, joint instability, stiffness and radiographic joint space narrowing35 are the main symptoms. Some other symptoms include joint swelling and limited motion range. Knee deformities such as valgus and varus often appear at a later stage with varus deformity more commonly seen because of the anatomical structure and dynamic tracks of knee movements.

The Kellgren–Lawrence grade (or K-L system) is a scoring tool used to assess the severity of knee OA on a [plain radiograph](https://en.wikipedia.org/wiki/Projectional_radiography%22%20%5Co%20%22Projectional%20radiography) 36. It was first proposed in 1957 by Drs. J.H. Kellgren and J.S. Lawrence37, described as follows:

0. No radiographic features of OA.

1. Possible joint space narrowing (normally at least 3mm) and osteophyte formation
2. Definite [osteophyte](https://en.wikipedia.org/wiki/Osteophyte%22%20%5Co%20%22Osteophyte) formation with possible [joint space](https://en.wikipedia.org/wiki/Joint_space%22%20%5Co%20%22Joint%20space) narrowing
3. Multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity
4. Large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity

MRI is not a routine examination for OA patients, but for OA research, it is a key-imaging tool38-40 as it is able to assess knee structures like menisci, ligaments, synovium, bone marrow, cartilage which are not visualized on common X-ray35, 41-44. In addition, it can detect early signs of OA. With MRI multiple tissue of the joint can be assessed simultaneously, and OA can be classified as hypertrophic and atrophic phenotypes45. MRI has also contributed to findings between pain and bone marrow lesions46 and synovitis47.

### Overview of risk factors for OA

From family-based studies, an inherited genetic predisposition of OA was known for many years48-50. Some studies have shown a hereditary basis that siblings specifically twins often have OA51.

Apart from hereditary factors, some other risk factors could be associated with OA’s development. Age, obesity, and sex hormone can influence knee OA directly. Excessive mechanical loading or physical activity, knee injuries and malnutrition can also contribute to joint degeneration52, 53

Age is one of the most common risk factors for OA. Age not only affects cartilage but also other tissues such as synovium, muscle and subchondral bone. These pathologies may alter joint loading. Some cell studies show that aging cells would increase cell senescence and affect mitochondrial function54-57.

Obesity has long been recognized to be associated with OA58, 59. Obese patients usually develop OA at younger age and their symptoms are more severe. A study suggested that obesity is correlated with knee OA as well as OA of other non-weight bearing joints and loss of body fat is more closely related to symptoms relief than loss of body weight. The results means obesity not only causes direct biomechanical contribution to knee OA but also some metabolic influences for the disease60.

Changes in sex hormone level may contribute to the progression of knee OA as the disease is more prevalent in post-menopausal females than males of the same age61, 62. An animal study shows that female hormone is protective but male hormone reduces protection 63.

In young adults’ OA, knee injury is the main cause. An injured knee has 4 times possibility to develop knee OA than a healthy one. Trauma caused damages to bone, cartilage, ligament and meniscus would all negatively affect knee joint stability64-68.

Herbeden’s nodes

Herbeden’s nodes are hard soft tissue or bony swellings that can develop in the [distal interphalangeal joints](https://en.wikipedia.org/wiki/Interphalangeal_articulations_of_hand%22%20%5Co%20%22Interphalangeal%20articulations%20of%20hand), and there seems to be a [genetic](https://en.wikipedia.org/wiki/Genetics%22%20%5Co%20%22Genetics) component involved in predisposition to the condition. They have been suggested to be associated with generalized OA69 and incidence/progression of knee OA as well as meniscus pathology70.

Meniscal tears

Meniscal tears can be traumatic or degenerative. Traumatic tears often appear as longitudinal or radial (with or without concomitant cruciate ligament injury) and are a result of increased force on a normal meniscus, such as internal rotation of the femur when the flexed knee moves toward an extend position. Degenerative tears are caused by normal forces on degenerative menisci and they usually appear as horizontal71. Traumatic and degenerative meniscus tears have different gene expression signatures72. Meniscal tears are more often found in the medial meniscus6, 73 maybe because the medial meniscus is less mobile and bears more forces under weight- bearing conditions compared with the lateral meniscus74, 75. Lateral meniscal tears are more frequently found in young patients who are more active with sports than older patients. They are usually accompanied by anterior cruciate ligament (ACL) tears76. The prevalence of meniscal tears increases with age6 and degenerative tears are much more common in senior people76. A study shows that asymptomatic meniscal tears are highly prevalent among middle - aged and older people77.

Meniscal extrusion

Meniscal extrusion is considered when the peripheral part of the mid portion (body) of the meniscus is markedly located outside the tibial joint margin. It is often regarded as pathological if the external margin of the meniscus exceeds the margin of the tibial plateau by >3 mm74, 78. When patients have advanced stages of meniscal degeneration or various types of meniscal tears, this abnormal extrusion degree is often seen74.

Meniscal extrusion is more functionally profound in medially because the medial compartment bears more weight-bearing and medial compartment abnormality is more prevalent than lateral compartment abnormality74. And I was aware of this during gathering meniscal extrusion data.

Meniscal extrusion and damage are also associated with cartilage pathology and are often found at an early stage of OA development74, 79. Tibiofemoral cartilage damage increases the risk of meniscal extrusion and conversely, meniscal extrusion would cause the femoral and tibial cartilage to impact each other, thus accelerating the development of knee OA80. A cross-section study points that radiographic joint space narrowing was found secondary to meniscal extrusion rather than thinning of articular cartilage81.

In several cross-sectional studies, meniscal extrusion were also reports to be associated with knee injury, gender, meniscal degeneration, extensive tears, knee alignment, cartilage damage, bone marrow lesions (BMLs) and obesity74, 82, 83.

Malalignment of lower limbs would alter normal loads on meniscal surface, and varus or valgus malalignment usually lead to medial or lateral meniscal extrusion, respectively84.

Similarly, meniscal sublaxation is caused by displacement away from or uncovering the tibial articular cartilage78 and meniscal derangement means those with disruption of the overall morphology of the meniscus and diffuse hyperintense signal in the body of the meniscus. MRI meniscal derangement was graded at each of three locations (anterior, central, and posterior horns) in the medial and lateral meniscus 85.

## Bone marrow lesion (BML)

BMLs are subcondral lesions characterized by increased bone volume fraction, thickened trabeculae 86 necrosis, sclerosis, edema and fibrosis 87. On MRI, it is described as ill-defined signal alterations adjacent to the subcondral plate88.(Figure 2) The occurrence of knee BMLs is either caused by acute knee trauma89, 90 or chronic reasons such as abnormal load transfer conditions91 or pharmaceutical effects92. A cross-sectional study by Gale *et al.* suggested a strong association between meniscal subluxation and ipsilateral BMLs78. Other longitudinal studies pointed out meniscal pathology such as maceration and extrusion as factors that increase the progression of BMLs structural alterations93, 94.

A recent study suggested that baseline meniscal extrusion and BMLs are associated with incident and progressive knee OA independently95.

Standard Radiography

Standard radiography such as X-ray is unable to directly show pathological changes of the meniscus, but is often used to exclude bony abnormalities and degenerative changes like joint space narrowing, loose body, osteophytes, subchondral bone cyst and sclerosis, which indirectly may suggest absence of normal meniscus integrity.



Figure 2:

Bone marrow lesion on coronal MRI slice (courtesy of Jos Runhaar)

## Magnetic Resonance Imaging

MRI is currently considered as the most accurate non-invasive clinical examination. It is much more Furthermore, the use of MRI after acute knee trauma may avoid a lot of diagnostic arthroscopic procedures96-98. MRI has become the gold standard for meniscal imaging. With MRI it is possible to characterize meniscal pathologies by type, extension, association with a cyst, meniscal extrusion and to evaluate cartilage and subchondral bone.

Some studies have shown excellent outcome regarding to sensitivity and specificity of MRI for diagnosing meniscal tears. The accuracy of MRI’s assessment for meniscal tear ranges from 82% to 95%99-104. Sensitivity and specificity of MRI are 93% and 88%, respectively for medial meniscal tears, 79% and 95% respectively for lateral meniscal tears105.

As to MRI field strength, 1.5 tesla machine is frequently used but recent years 3.0 tesla machines are becoming more and more prevalent in hospitals and institutes. Some studies state 3.0 T should result in more detailed images and increase the diagnostic accuracy106, 107. But 3T imaging also has some disadvantages such as increased sensitivity to metallic artefacts.

The MRI images should be taken on all three planes: sagittal, coronal and axial. But not all sequences should be taken on all planes. T1-weighted sequences are usually performed on the sagittal plane and T2-weighted sequences are performed on all three spatial planes108.

Spin-echo or fast spin-echo proton density with or without fat saturation, gradient echo and T1 are the most commonly used sequences109. However, different structures require different MR pulse sequences for the optimal assessment. For example, BMLs and focal cartilage defects are best assessed by fluid-sensitive fast spin echo sequences (e.g. T2-weighted, proton density-weighted or intermediate-weighted) with fat suppression110, 111. Meniscus is best assessed by proton density-weighted (FSE) sequences and T2-weighted and fast spin-echo T-weighted sequences112, 113 as well as FSE Rhô Fat Sat sequences.

Several semiquantitative MRI scoring systems have been developed, e.g. The Whole Organ Magnetic Resonance Imaging Score (WORMS), (MRI review 26), the Knee Osteoarthritis Scoring System (KOSS), (S8) the Boston Leeds Osteoarthritis Knee Score (BLOKS), and a new scoring system called the MR Imaging Osteoarthritis Knee Score (MOAKS) 114. In my papers II, meniscal tear was assessed by MOAKS and in paper III BMLs was assessed by MOAKS as well.

MRI has some advantages:

1. MRI is painless.
2. The joints do not need to be manipulated.
3. The procedure can be performed in 20 minutes.
4. Very useful to diagnose residual meniscal lesions after surgery.

MRI also has some disadvantages and contradictions:

1. Some patients can not undergo MRI scan procedures: obese patients over 170 kg, claustrophobic patients, or patients with pace-makers or recent stents, etc.. But open MRI machines and extremity MRI units has reduced the number of obese and claustrophobic patients who can not undergo MRI.
2. It would be influenced by nearby orthopedic hardwares such as bioabsorbable screws.

##

## Treatment

### Treatment of meniscal tear

The menisci are easily injured and difficult to repair. Early onset of OA was noted to be associated with meniscus injuries and meniscectomy is often performed when OA signs appear115, 116. The aim of surgical treatment for meniscal tears includes alleviation of pain, recovery to normal activities and prevention of premature degenerative developments of knee.

### *Repair of meniscal tear*

A British surgeon, Thomas Annandale pioneered the surgical treatment of meniscal tear in late 19th century. He performed the first recorded suture of meniscal tear in 1885117 and published another report of total meniscectomy in 1889118. Then total meniscus excision dominated the surgical treatment methods for over 80 years as meniscus was regarded as a functionless part in the knee joint119. However, accelerated osteoarthritic signs e.g. cartilage loss, narrowed joint space and flattened femoral condyles were found radiologically on knees after total meniscectomy over time120.

The choices of treatment methods for meniscal tears depend on many factors such as types, locations and sizes of the lesions. As aforementioned, asymptomatic meniscal tears are widely found on knee MRIs of middle-age and older people, these cases usually need no treatment77. Not all types of meniscal tears are feasible for repair due to limited blood supply of meniscus. Radial tears, flaps and degenerative tears are generally not repaired 121, 122. Peripheral, longitudinal, oblique and unstable tears are often suitable to be repaired but horizontal, radial and complex tears are not amenable for repair123, 124. After repair procedure, the operated knees should be kept non- or partially weight bearings for weeks. After Partial meniscectomy, less time is needed for full body weight bearing123. It usually takes 4 months for the tissue to heal and for the patients to feel no symptoms. The locations and types of tears often affects long-term outcomes of meniscal repairs6.

Some prospective factors for favourable repair outcome include: younger age (under 30 years old), the length of tear (0-2 cm), a lateral meniscus tear, a peripheral tear and simultaneous ACL reconstruction with meniscus repair procedure6, 123. The concomitant ACL reconstruction procedures yielding better healing was believed that surgical tunnels lead to intra-articular bleeding125-127 and this surgical treatment increase the stability of knee128. Clinically, it is important to distinguish whether a meniscal tear is repairable or not, specifically for athletes who usually have repeated stress could turn a potentially repairable meniscal tear into an irreparable one123.

In contrast to meniscectomy procedures (partial or complete), meniscal repair could preserve the biomechanics of meniscus as much as possible123, 124, 129. However, the long term-outcome of repair vs meniscectomy is still controversial. There are yet no randomized control trials (RCTs) in this field.

Before meniscal repair, certain preparatory procedures should be carried out: removal of loose meniscal fragments and trimming of frayed meniscal edges in order to facilitate the healing process121, 126. Local synovium abrasion is recommended too.

Meniscal repair techniques include classic inside-out and outside-in suture techniques and more advanced devices such as anchors and sliding knots. Sometime, combined surgical techniques are used to stabilize a particular meniscal tear. Some risky complications include nerve and vascular injuries and it is not easy to access the anterior parts of menisci 121.

### *Knee arthroscopy*

From 1970s, arthroscopy has been generally adopted to diagnose and treat a wide range of knee problems. Knee arthroscopy is currently the gold standard to diagnose and treat meniscal disorders. During arthroscopy, the surgeon can see the structures of the knee in great detail on a video monitor. Arthroscopic probing is often used to evaluate the tear size, instability, tissue quality, tear zone (i.e., red-red, red-white, white-white) as well as the width and integrity of the meniscal rim130. However, arthroscopic findings are not always consistent with pre-surgery MRI results131. A study showed that compared with arthroscopy, MRI scanning had a sensitivity of 90.5%, specificity of 89.5%, and an accuracy of 90.1%132. The advantages of knee arthroscopy include less invasiveness to skin and soft tissues, less pain and joint stiffness after surgery and reduced recovery time compared to traditional open knee surgery.

### *Partial meniscectomy*

In 1947 Lipscomb and Henderson reported partial meniscectomy yielded equally good outcomes in short term and suggested it as an alternative choice to total excision29.

Partial meniscectomy is less detrimental to knee joint compared with total meniscectomy for treating unstable meniscal tears6. If a meniscus tear can not be satisfactorily sutured, partial meniscectomy is still recommended133, 134. The ideal result is to keep the meniscal tissue as much as possible, specifically the outer 1/3 part which has better vascularization, only resect the unstable part. But in practical application, part of the stable tissue is removed as well in order to keep meniscus’s original shape and avoid leading to abnormal stress to the remaining part of meniscus135. However, similar to total meniscectomy, partial meniscectomy is also associated with the development of degenerative changes over time136. The reason for this may be changed biomechanics of the meniscus. The remaining part of meniscus bears more stress and has less transmission ability of hoop stresses137.

Physicians usually suggest patients with knee joint symptoms and a meniscal tear to be treated with arthroscopic partial meniscectomy (APM) for reducing knee pain and improving knee functions. For many years this surgical treatment has been widely used for treatment of meniscal tears, traumatic as well as degenerative138-142. However, several randomized controlled trials (RCTs) recently have roused discussions about the efficacy of APM, pointing out non-surgical treatments could as well relief knee symptoms or improve knee functions equivalently143-147. A recent review even showed APM was not a better choice in comparison with physical therapy for treating patients with symptomatic meniscal tear in aspects of knee pain relieving, knee functions improvement, etc.148. Moreover, it is still controversial whether APM would accelerate the development of patients’ risk of knee OA more significantly than conservative regimens149-152.

### Meniscus transplantations

Autologous meniscal transplantation is commonly applied in younger patients whose meniscal lesions are irreparable or who previously have undergone partial meniscectomy135. Meniscal allograft transplantation and the use of synthetic implants have been reported yielding promising outcome on symptomatic patients who have undergone a partial, subtotal or total meniscectomy153. Meniscal transplantation is often operated concomitantly with other surgeries such as cartilage repair, cruciate ligament reconstruction and high-tibial osteotomies154.

###

### Conservative treatment

It is controversial whether surgical treatment is superior to conservative methods such as physical therapy. Some studies pointed that arthroscopy procedure may accelerate knee OA development74, 78. However, a meniscal tear would enlarge over time if leaving a degenerative meniscus tear *in situ,* causing more loss of meniscus function. This point is also a question this thesis aims to look into.

# Aims of study

### General aim

To investigate risk factors for meniscal extrusion such as gender, body mass index (BMI), knee injuries and meniscal resection as well consequences of meniscal extrusion with respect to development of bone marrow lesions.

### Specific aims

* To determine risk factors associated with increased meniscal body extrusion on knee magnetic resonance (MR) images in subjects free of radiographic OA. (Paper I)
* To determine factors associated with higher degree of meniscal body extrusion in overweight and obese women at high risk of knee OA. (Paper II)
* To determine the association between meniscal body extrusion and bone marrow lesion development/enlargement in overweight and obese women at high risk of knee OA. (Paper III)
* To determine the effect of APM on medial meniscal body extrusion in patients with OA and meniscal tear. (Paper IV)

# Subjects and methods

## Osteoarthritis Initiative (OAI)

The Osteoarthritis Initiative (OAI) database is a large multi-center, longitudinal, prospective observational ongoing study cohort, sponsored by National Institutes of Health (NIH) (part of the Department of Health & Human Services), aiming at characterizing risk factors related to the onset and development of symptomatic knee OA and at identifying biomarkers of the disease. The database is available for public access at <http://www.>oai.ucsf.edu/. The overall aim of the OAI is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for OA as potential surrogate endpoints for disease onset and progression.

Four clinical centers and a data coordinating center will conduct the OAI, public-private partnership that will bring together new resources and commitment to help find biochemical, genetic and imaging biomarkers for development and progression of OA. The OAI establishes and maintain a natural history database for OA that will include clinical evaluation data, radiological (x-ray and magnetic resonance) images, and a biospecimen repository from 4796 men and women ages 45-79 enrolled between February 2004 and May 2006.

Four 3.0 Tesla MRI scanners, one at each clinical center, are dedicated to imaging the knees of OAI participants annually over four years. The seven-year project has recruited participants who have, and those who are at high risk for developing, symptomatic knee OA.

The OAI consortium includes public funding from the NIH and private funding from several pharmaceutical company partners managed by the Foundation for the NIH.

The OAI is an unparalleled state-of-the-art database showing both the natural progression of the disease and information on imaging and biochemical biomarkers and outcome measures.

The OAI was approved by the respective institutional review boards for the University of California, San Francisco and the four OAI clinical centers (University of Pittsburgh, Ohio State University, University of Maryland, Baltimore, Memorial Hospital of Rhode Island). Informed consent was obtained from all participants in accordance with the declaration of Helsinki.

Paper I was based on a sample of 340 chosen subjects from OAI according to criteria below.

* Age between 45 and 55 years old.
* Both knees’ K-L grade = 0 at baseline according to central readings.
* Knee MRIs available at all four time points (baseline, 24 months, 48 months, 72 months, all four time points were used for meniscal integrity assessment.)

The search resulted in 340 subjects.

Table 1.

Characteristics of my OAI cohort study subjects at baseline

|  |  |
| --- | --- |
| **Characteristic** | **N = 340** |
| Women, n(%) | 173 (51) |
| Age, mean SD (range) years | 50.4 ± 3.0 (45 - 55) |
| Body mass index, mean SD (range) kg/m2 | 26.7 ± 4.4 (18.4 - 41.6) |
| Medial meniscal tear, n (%) |  |
|  Right knee | 42 (12.4%) |
|  Left knee | 50 (14.7%) |
| Larteral menescal tear, n (%) |  |
|  Right knee | 20 (5.9%) |
|  Left knee | 13 (3.8%) |
| OAI inclusion cohort, n (%) |  |
|  Progression subcohort | 16 (5) |
|  Incidence subcohort | 278 (82) |
|  Reference subcohort | 46 (14) |
| Baseline extrusion ratio-medial meniscus, mean (SD) |  |
|  Right knee | 3.43 (1,23) |
|  Left knee | 3,23 (1,15) |
| Baseline extrusion ratio-lateral meniscus, mean (SD) |  |
|  Right knee | 1,54 (1,31) |
|  Left knee | 1,54 (1,31) |

## Prevention of Knee Osteoarthritis in Overweight Females (PROOF)

The PROOF study is a Netherlands-based trial. This trial included 407 women between 50 and 60 years without knee complaints, but with a BMI ≥ 27 at baseline. During a 30 months follow-up period (only 10% drop-outs) the effects of a diet & exercise program and of glucosamine sulphate in a 2x2 factorial design were evaluated. At baseline and after 30 months an extensive set of measurements were performed, with some additional measurements every 6 months.

MRIs of both knees were acquired at baseline on 1.5 T scanners. The MRI protocol included coronal and sagittal non-fat suppressed proton density weighted sequences (slice thickness 3.0 mm/slice gap 0.3 mm), a coronal T2 weighted Spectral Presaturation by Inversion Recovery sequence (slice thickness 5.0 mm/slice gap 0.5 mm), an axial dual spin-echo sequence (slice thickness 4.5 mm/slice gap 0.5 mm) and a sagittal 3D water selective sequence with fat saturation (slice thickness 1.5 mm).

PROOF trial was approved by the ethics committee at the Erasmus University Medical Center Rotterdam, the Netherlands in 2005.

Paper II is based on the baseline data of PROOF study. During the progress of reading images, I found 12 subjects’ MR images were incomplete (with only one sided knee images) or unreadable. Therefore, the final number of subjects analysed was 395.

Table 2. Characteristics of the PROOF trial subjects

|  |  |
| --- | --- |
| **Women** | **N=395** |
| Age, mean (SD) years | 55.7 (3.2) |
| Body mass index, mean (SD) kg/m2 | 32.4 (4.3) |
| Physical activity\*, mean (SD)  | 6837 (3714) |
| Postmenopausal status | 68% |
| Heberden’s nodes | 26% |
| **Knees** | **N=790** |
| Varus malalignment | 40% |
| Valgus malalignment | 12% |
| History of knee injury | 13% |
| Kellgren-Lawrence grade ≥1 | 50% |
| Quadriceps muscle strength, mean (SD) Newton | 253 (47) |
| Mild knee symptoms | 31% |
| Meniscus tear, medial | 9% |
| Meniscus tear, lateral | 5% |

\*Measured with the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) questionnaire

Paper III is based on the baseline and the 30 months follow-up of PROOF study (longitudinal data)

## **METEOR trial**

The METEOR trial (ClinicalTrials.gov number, NCT00597012) is a multi-center randomized controlled trial that involved 351 patients aged 45 or older with knee symptoms and meniscal tear as well as knee OA detected on MRI or radiography. Details of inclusion and exclusion criteria, and interventions provided have been published elsewhere. In brief, the subjects were randomized either to undergo APM or physical therapy stratified according to sex and the extent of OA on baseline radiography (either K-L grade 0 to 2 or K-L grade 3). Cross-over from physical therapy to APM due to treatment failure was allowed.

The study was approved by the Partners HealthCare Human Research Committee and overseen by a data and safety monitoring board assembled by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Paper IV was based on data of METEOR trial

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## MRI measurements

I used Sante DICOM Editor (64-bit) software. In all four studies, I gathered data of tibial plateau width from the margin of the tibial plateau excluding any possible osteophytes, medial and lateral meniscus coronal width, and meniscal body extrusion to the closest 0.1 mm. These data were all measured on ‘mid-coronal’ MRI slices which I refer to the single slice visually showing the greatest area of the medial tibial spine. If this was difficult to differentiate because two slices may depict a similar area of the tibial spine, I used the slice which showed the greatest width of the tibial plateau. The two-dimensional quantitative measurement technique I took was original developed by Hunter et al 79.（Figure 3 ）



Figure 3.

Example of measurements on mid-coronal 1.5 T intermediate weighted knee magnetic resonance images using Sante DICOM Editor

## Meniscal tear reading

In paper I, one musculoskeletal radiologist assessed four time points’ meniscal tear (baseline, 24 months, 48 months, 72 months.) using the IW TSE sagittal and coronal fat-suppressed sequences. If an increased meniscal signal communicated with the superior, inferior or free edge of the meniscal surface (or more complicated) on at least two consecutive images (Or if a tear was visible on both sagittal and coronal images), it is considered a radial tear 155.

In paper II, meniscal tears were read using the MOAKS scoring system (the MRI Osteoarthritis Knee Score), a semi-quantitative MRI OA scoring method with high inter-observer reliability156, 157.

## Bone marrow lesions reading (Paper III)

BMLs reading was done by two trained readers as well as an experienced musculoskeletal radiologists also using MOAKS.

The time line sequence was known by the readers, but the clinical details were blinded to them. Both baseline and 30 month follow-up MRI images were read at the same occasion. During the reading process, BMLs’ evolution was defined by definitions published in previous report114.

For each MOAKS defined subregion in the tibiofemoral compartment, incidence/progression of BML over the following time was defined as either the incidence of a cyst or a BML in a compartment without baseline BML , or score’s increase for the size of the BML, or the number of BMLs’ increase in the compartment when size was unchanged.

## Meniscal body extrusion ratio

In order to take into account of different knee sizes, e.g. men and women (the sizes even vary significantly in the same sex.), I used a meniscal body extrusion ratio calculated as [meniscus body extrusion]/[tibia width]\*100. (Paper I)

## Statistical analysis

In my longitudinal OAI cohort study (paper I), the hypothesized risk factors were evaluated by a multivariable linear regression mixed model. Based on previous reports and/or evidence from cross-sectional data74, 82, 83, sex, age, the baseline extrusion index, baseline BMI and incident meniscal tear during follow-up were chosen as risk factors for analysis. In that way a quantitative outcome measure was used to evaluate the change in meniscus body extrusion (on the continuous scale). Mechanical knee alignment was also included as a covariate in an additional model on a subcohort including 243 subjects (480 knees). These knees have available baseline mechanical knee alignment data and a sensitivity analysis was made in which change in BMI was included. I did not include knee alignment in the primary model as 30% of the data were missing. Knee alignment was categorized into three categories by the hip-knee-ankle angle from OAI full-limb X-ray according to rules reported by Felson *et al.*158: normal, varus or valgus. OAI clinical site was also adjusted a random intercept on a person level was included to take into account the correlation between knees in the same person. The model assumptions were checked by residual plots. The data were presented with the estimate of association (the extrusion ratio change) and its 95% confidence interval (95% CI). (SPSS software version 21, and STATA 12).

In my cross-sectional PROOF study (paper II), BMI (continuous), age (continuous), physical activity (continuous), menopause status (yes/no), Herberden’s nodes (yes/no), knee alignment (categorical), K-L grade (0 vs ≧1), history of knee injury (yes/no), ipsilateral meniscus tear (yes/no), and quadriceps muscle strength (continuous) were hypothesized as risk factors and evaluated. Firstly, a random effects linear regression model with robust standard errors was used to analyze the association of these risk factors with medial and lateral extrusion respectively. All analyses were adjusted for the tibial plateau width as well. In a second step, a fixed effects linear regression model was used to analyze the association of the knee-specific risk factors with medial and lateral extrusion.

In the other PROOF study (paper III), I also used two types of statistical models. The primary model was a random effects logistic regression which included all persons with non-missing data. Several person-specific covariates were adjusted: body height, body weight, age and physical activity as well as knee specific covariates: tibial width, knee alignment and ipsilateral meniscus damage. This model was repeated with adjustment for knee injury during the follow-up period as sensitivity analysis. The secondary model was a fixed effects logistic regression which included persons with discordant knee outcome. In this model only knee-specific covariates were included and this model was considered as a form of additional sensitivity analysis to evaluate if the results of the random-effects model could be confounded by unmeasured person-specific factors. The estimates were presented as odds ratio (ORs) with 95% CIs. These ORs can be regarded as risk ratios because the occurrence of incidence/enlarging BMLs was low.

For the METEOR study (paper IV), intention to treat (ITT) principle was used as primary analysis. Per-protocol analysis was also performed. The mean difference in extrusion was evaluated by t-test. All tests were 2-tailed and a p<0.05 was considered as statistically significant (IBM SPSS Statistics Version 22).

# Results and discussion

## Risk factors for increased meniscal body extrusion in knees free of radiographic OA – a longitudinal study

In my longitudinal OAI cohort study, 340 subjects (167 men and 173 women) were chosen according to certain criteria. The mean (SD) age of these subjects was 50.4 (3.0) years. The total number of knees was 680. (Table 1) At baseline, 92 of 680 menisci (13.5%) and 33 of 680 lateral menisci (4.9%) in 119 of 680 knees (17.5%) of 96 subjects (28.2%) were found to have non-displaced meniscal tears. Only one knee had an incident maceration but without incident tears. All other menisci with maceration had tears.

Mean (SD) medial extrusion ratio in the right knee at baseline and 72 months were 3.43 (1.23) and 3.32 (1.30), respectively (similar values in the left knee). The corresponding values for lateral compartment were 1.54 (1.31) and 1.13 (1.52).

In medial compartment, female sex was found to be significantly associated with increased meniscal extrusion ration in contrast to men, with extrusion ratio change = 0.35 (95% CI: 0.16, 0.53) which means extrusion ratio of women at 72 months was 35% greater than that of men. Incident meniscal tear during the 72 months period was another significant risk factor for increased extrusion ratio with extrusion ratio change = 0.29 (95% CI: 0.02, 0.55). Moreover, baseline extrusion ratio was also significantly associated with increased medial meniscal extrusion ratio with extrusion ratio change = 0.63 (95% CI: 0.56, 0.70). However, neither BMI nor age was found to be significantly associated with change in meniscal extrusion ratio. And knee alignment and BMI change were not statistically significant in the sensitivity analyses. (Table 2)

Similarly, in the lateral compartment, female gender was also found significantly associated with increased meniscal extrusion ratio with extrusion ration change = 0.21 (95% CI: 0.04, 0.37), baseline extrusion index with extrusion ratio change = 0.77 (95% CI: 0.71, 0.83), incident ipsilateral tear with extrusion ratio change = 0.29 (95% CI: 0.02, 0.55). And BMI, age, knee alignment and change in BMI were found to have statistically significant associations with increased meniscal extrusion ratio either. (Table 3)

Female gender was found to be a risk factor for increased meniscal extrusion in both medially and laterally. It is commonly known female knee OA is more frequent than male knee OA43, 159, 160 and often develops faster43. The exact reasons for these are not fully confirmed. The founding of my study also provides novel longitudinal evidence that meniscus extrusion may contribute to the onset and progression of knee OA. It is speculated that hormonal condition in post-menopausal women may cause laxity of collateral ligaments which could lead to deteriorated meniscus body extrusion, reduced meniscal extrusion and increased abnormal contact stress on cartilage161, 162.

Menisci’s normal structure includes circumferential oriented collagen fibers woven with radial fibers which function like tension rods to keep shape and structure when the meniscus is axially loaded163. So a meniscal tear may compromise the hoop tension so in such pathological condition meniscal extrusion may aggravate under normal perpendicular loading.

Table 3

Risk factors for increase in medial extrusion ratio\* by 72-month follow-up of paper I

|  |  |  |
| --- | --- | --- |
| **Risk factor - main model** | **Extrusion ratio change†** | **Extrusion ratio change‡** |
|  | (95% confidence interval) | (95% confidence interval) |
| Baseline body mass index |  |  |
|  18-24 | Reference category | Reference category |
|  25-29 | -0.22 (-0.49, 0.06) | -0.18 (-0.38, 0.02)  |
|  30+ | -0.40 (-0.73, -0.07) | -0.10 (-0.34, 0.14)  |
| Age | -0.03 (-0.07, 0.01) | -0.01 (-0.03, 0.03)  |
| Gender |  |  |
|  Male | Reference category | Reference category |
|  Female | 0.55 (0.31, 0.79) | 0.35 (0.16, 0.53)  |
| Incident meniscal tear | 0.14 (-0.17, 0.45) | 0.29 (0.02, 0.55) |
| Baseline extrusion ratio | 0.64 (0.57, 0.71) | 0.63 (0.56, 0.70)  |
| Risk factor - sensitivity analyses |  |  |
| Knee alignment§ |  |  |
|  Normal | Reference category | Reference category |
|  Valgus | 0.09 (-0.27, 0.45) | 0.02 (-0.28, 0.32)  |
|  Varus | 0.08 (-0.18, 0.33) | 0.15 (-0.07, 0.36)  |
| Change in BMI | -0.03 (-0.09, 0.04) | -0.01 (-0.05, 0.04)  |

\* [medial meniscus body extrusion]/[tibia width]×100. † Crude estimates. ‡ Adjusted for all covariates listed in the table and for the study site. §Model on a subset of 243 subjects (480 knees) with baseline mechanical knee alignment available.

And past reports also suggest meniscal tear especially root tear often co-occur with meniscal extrusion74.

BMI was not found to be a risk factor for change of meniscal extrusion ratio in paper I. Although it was reported to be a risk factor for the development of medial meniscal extrusion70, Crema *et al.* suggested BMI itself would have no effect on meniscal position, just affects other concomitant risk factors83.

Table 4

Risk factors for increase in lateral extrusion ratio by 72-month follow-up of paper I

|  |  |  |
| --- | --- | --- |
| **Risk factor - main model** | **Extrusion ratio change†** | **Extrusion ratio change‡** |
|  | **(95% confidence interval)** | **(95% confidence interval)** |
| Baseline body mass index |  |  |
|  18-24 | Reference category | Reference category |
|  25-29 | 0.16 (-0.15, 0.47) | 0.12 (-0.06, 0.30)  |
|  30+ | 0.28 (-0.09, 0.66) | 0.13 (-0.09, 0.35)  |
| Age | -0.04 (-0.09, 0.00) | -0.02 (-0.05, 0.01)  |
| Gender |  |  |
|  Male | Reference category | Reference category |
|  Female | 0.24 (-0.04, 0.52) | 0.21 (0.04, 0.37)  |
| Incident meniscal tear | 0.31 (-0.16, 0.77) | 0.29 (0.02, 0.55) |
| Baseline extrusion ratio | 0.77 (0.71, 0.83) | 0.77 (0.71, 0.83)  |
| Risk factor - sensitivity analyses |  |  |
| Knee alignment§ |  |  |
|  Normal | Reference category | Reference category |
|  Valgus | -0.03 (-0.40, 0.33) | -0.17 (-0.46, 0.11)  |
|  Varus | 0.01 (-0.25, 0.27) | -0.11 (-0.31, 0.10)  |
| Change in BMI | -0.03 (-0.10, 0.05) | -0.01 (-0.04, 0.04)  |

\* [medial meniscus body extrusion]/[tibia width]×100. † Crude estimates. ‡ Adjusted for all covariates listed in the table and for the study site. §Model on a subset of 243 subjects (480 knees) with baseline mechanical knee alignment available.

### Risk factors for meniscal body extrusion on knee MRI in overweight and obese women – a cross-sectional study

In my cross-sectional study on PROOF database, the mean (SD) of the 395 study participants was 55.7 (3.2) years and the mean (SD) BMI was 32.4 (4.3) kg/m2. Among all 395 women, 267 (68%) were post-menopausal, 104 (26%) had Heberden’s nodes. Of the 790 knees, 313(40%) were varus and

98 (12%) were valgus, 246 (31%) had an affirmative answer to pain in or around the knee during the past 12 months, 100 (13%) had an injury history, and 393 knees (50%) had K-L grade≧1 (49 knees with KL grade 2 and 5 knees with KL grade 3) (Table 2).

Among all the 790 knees, 181 (23%) had medial meniscus extrusion ≧3.0 mm. In the univariable analysis, high BMI, Heberden’s node, meniscal tear, varus malalignment, knee injury history, mild knee symptoms and KL grade ≧1 were statistically significantly associated with high degree of medial meniscal body extrusion. In the multivariable random effects analysis, the medial meniscus extrusion was higher in persons with higher BMI by 0.20 mm (95% CI 0.05, 0.35), with mild knee symptoms 0.25 mm (95% CI 0.05, 0.44), meniscal tear 0.44 (95% CI 0.11, 0.77) and KL grade ≧1 0.43mm (95% CI 0.26, 0.60) (Table 6). The estimates of associations remained similar in the analysis of knee-specific risk factors when adjusting for all the person level confounding.(Table 7)

Only 4% of all the 790 available knees were found to have lateral meniscal extrusion ≧3.0 mm. No statistically significant associations with the included risk factors were found in the multivariable regression model. But I found KL≧1 was associated with increased lateral extrusion by 0.35 mm (95% CI 0.10, 0.60) when accounting for the person-level confounding. And the lateral extrusion was decreased by 0.17 mm (95% CI 0.08, 026) per mm increase in tibia width.

Although Crema *et al.* suggested that BMI itself has no effect on meniscus position83 but the change of BMI would affect other concomitant risk factors like meniscus tear, cartilage damage and knee alignment, I hypothesize it would have potentially a more direct effect on meniscus position in some subjects. There was a report that diet and exercise program for reducing weight had affected the progression of meniscus extrusion over 30 months follow-up164. But whether this would reduce future knee OA development is still unknown.

Knee injury was reported to be strongly linked to meniscus tear157, 159 and this cross-sectional study confirmed it is associated with meniscus extrusion as well. Knee trauma often compromise the integrity of knee joint structures like menisci thus reduce the hoop tension and increase risk of meniscus extrusion19.

In both random-effects and fixed effects linear regression analysis K-L grade is a risk factor for medial extrusion and the fixed-effects linear regression analysis showed it is a risk factor for lateral meniscal extrusion as well. Subjects with K-L ≥1 have structural changes indicative of OA and joint space narrowing is a part of the grading system. A couple of reports have also suggested that meniscus conversely contribute to joint space narrowing on radiographs79, 165.

Heberden’s nodes are hard soft tissue or bony swellings often found around the distal interphalangeal joints. It is regarded to be associated with generalized OA and strong genetic determinants69. And they have been reported to be connected with the incidence and progression of knee OA166 as well as meniscus pathology70. But in my cross-section PROOF study, no statistically significant associations were found between meniscal extrusion and Heberden’s nodes.

In my cross-sectional PROOF study, quadriceps muscle strength was not found to be associated with meniscal body extrusion although a systematic review reported weak knee extensor muscle is associated with a higher risk of developing knee OA in both genders167.

### Bone marrow lesions and meniscal body extrusion

The same baseline PROOF subjects were used in this study (paper III), with the mean (SD) of the 395 study participants was 55.7 (3.2) years and the mean (SD) BMI was 32.4 (4.3) kg/m2. Of the 790 knees, 299 (37.8%) were valgus, 246 (31.1%) had an affirmative answer to pain in or around the knee during the past 12 months, 100 (13%) had an injury history, and 393 knees (50%) had KL grade≧1 (49 knees with K-L grade 2 and 5 knees with K-L grade 3). (Table 2)

The outcome value (incident/enlarging BMLs in the tibiofemoral compartment) was missing in 68 persons (17%), 127 knees (16%) and 254 compartments (16%), mainly due to no knee MRI obtained at the follow-up time point.

In the primary analysis (random-effects regression), 63 knees had an incident/enlarging BML with a multivariable OR of 1.24 (95% CI 0.99, 1.57) for the medial meniscal extrusion parameter, i.e. a 24% increased likelihood of incident/enlarging BML per 1 mm extrusion. The sensitivity analysis with adjustment for knee injury yielded the OR of 1.27 (95% CI 1.02, 1.59).

The multivariable effect estimate from the fixed-effect regression model was similar (OR 1.19, 95% CI 0.81, 1.76) for the medial meniscal extrusion parameter suggesting that there was no substantial confounding from unmeasured person-level factors.

Table 5

The random-effects linear regression analysis (univariable analyses) of paper II.

|  |  |  |
| --- | --- | --- |
|  | **Medial** | **Lateral** |
| Age | 0.02 (-0.01, 0.05) | 0.01 (-0.02, 0.04) |
| Body mass index, per 5kg/m² increase | 0.25 (0.13, 0.36) | 0.00 (-0.11, 0.11) |
| Physical activity, per 1 SD | 0.04 (-0.05, 0.14) | 0.04 (-0.06, 0.13) |
| Menopause | -0.10 (-0.32, 0.11) | -0.07 (-0.28, 0.15) |
| Heberden’s nodes | 0.23 (0.01, 0.46) | 0.20 (-0.02, 0.42) |
| Knee alignment: Neutral  | reference | reference |
|  Varus | 0.27 (0.09, 0.45) | 0.00 (-0.17, 0.18) |
|  Valgus | -0.15 (-0.40, 0.10) | 0.14 (-0.10, 0.37) |
| History of knee injury | 0.25 ( 0.02, 0.49) | 0.19 (-0.03, 0.42) |
| Kellgren-Lawrence grade ≥1 | 0.54 (0.38, 0.71) | 0.14 (-0.03, 0.30) |
| Quadriceps strength, per 1 SD increase | 0.02 (-0.07, 0.11) | 0.01 (-0.07, 0.10) |
| Mild knee symptoms | 0.38 (0.21, 0.55) | 0.10 (-0.06, 0.27) |
| Ipsilateral meniscus tear | 0.53 (0.26, 0.80) | 0.28 (-0.06, 0.62) |

Table 6

The random-effects linear regression analysis (multivariable analysis); model adjusted for tibia width.

|  |  |  |
| --- | --- | --- |
|  | **Medial** | **Lateral** |
| Age | 0.01 (-0.02, 0.05) | 0.01 (-0.02, 0.05) |
| BMI, per 5kg/m² increase | 0.20 (0.05, 0.35) | -0.01 (-0.14, 0.12) |
| Physical activity, per 1 SD | 0.05 (-0.05, 0.15) | 0.00 (-0.12, 0.11) |
| Menopause | -0.13 (-0.36, 0.10) | -0.12 (-0.35, 0.11) |
| Heberden’s nodes | 0.17 (-0.05, 0.38) | 0.20 (-0.03, 0.44) |
| Knee alignment: Neutral  | reference | reference |
|  Varus | 0.17 (-0.02, 0.35) | -0.05 (-0.22, 0.13) |
|  Valgus | -0.19 (-0.42, 0.05) | 0.15 (-0.18, 0.48) |
| History of knee injury | 0.06 (-0.19, 0.32) | 0.13 (-0.14, 0.40) |
| Kellgren-Lawrence grade ≥1 | 0.43 (0.26, 0.60) | 0.13 (-0.05, 0.30) |
| Quadriceps strength, per 1 SD increase | 0.03 (-0.07, 0.13) | 0.07 (-0.03, 0.17) |
| Mild knee symptoms | 0.25 (0.05, 0.44) | 0.11 (-0.08. 0.29) |
| Ipsilateral meniscus tear | 0.44 (0.11, 0.77) | 0.26 (-0.18, 0.70) |

Table 7

The fixed-effects linear regression analysis (univariable analyses) of knee-specific risk factors.

|  |  |  |
| --- | --- | --- |
|   | **Medial** | **Lateral** |
| History of knee injury | 0.28 (-0.03, 0.60) | 0.20 (-0.08, 0.49) |
| Kellgren-Lawrence grade ≥1 | 0.40 (0.14, 0.66) | 0.29 (0.05, 0.53) |
| Quadriceps strength, per 1 SD increase | -0.03 (-0.21, 0.14) | -0.01 (-0.17, 0.15) |
| Knee alignment: Neutral  | reference | reference |
|  Varus | 0.27 (0.09, 0.45) | 0.00 (-0.17, 0.18) |
|  Valgus | -0.15 (-0.40, 0.10) | 0.14 (-0.10, 0.37) |
| Mild knee symptoms | 0.38 (0.15, 0.62) | 0.14 (-0.08, 0.35) |
| Ipsilateral meniscus tear | 0.38 (0.02, 0.73) | -0.10 (-0.53, 0.32) |

Table 8

The fixed-effects linear regression analysis (multivariable analysis) of knee-specific risk factors; model adjusted for tibia width.

|  |  |  |
| --- | --- | --- |
|  | **Medial** | **Lateral** |
| History of knee injury | 0.11 (-0.20, 0.43) | 0.09 (-0.20, 0.39) |
| Kellgren-Lawrence grade ≥1 | 0.43 (0.17, 0.69) | 0.35 (0.10, 0.60) |
| Quadriceps strength, per 1 SD increase | -0.04 (-0.22, 0.13) | 0.03 (-0.14, 0.19) |
| Knee alignment: Neutral  | reference | reference |
|  Varus | 0.13 (-0.14, 0.40) | 0.04 (-0.22, 0.29) |
|  Valgus | -0.27 (-0.60, 0.06) | 0.19 (-0.12, 0.50) |
| Mild knee symptoms | 0.24 (-0.01, 0.49) | 0.10 (-0.13, 0.34) |
| Ipsilateral meniscus tear | 0.29 (-0.07, 0.65) | -0.19 (-0.62, 0.23) |

In the primary random-effects regression analysis for lateral meniscus 42 knees had an incident/enlarging BML with a multivariable OR of 1.69 (95% CI 1.27, 2.25) per 1 mm larger extrusion. The sensitivity analysis with additional adjustment for knee injury yielded the effect estimate of 1.70 (95% CI 1.27, 2.26) (Table 9).

The multivariable fixed-effects analysis confirmed the findings from the primary model with an OR of 1.89 (95% CI 1.08, 3.31) for the lateral meniscal extrusion parameter.

The pathogenesis of BMLs is still not completely clear. It is hypothesized to represent focal excessive pathological loading. A previous longitudinal study of the Multicenter Osteoarthritis Study (MOST) dataset suggested higher relative risks were associated with more severe and with lateral meniscal pathology 94. The outcome of paper III has similar conclusion that there is a slightly stronger association between lateral meniscal extrusion and BML development. It seems abnormal lateral meniscus position is more detrimental to meniscus functions compared with medial meniscus as lateral meniscus’s role in load distribution and the anatomical structure of more concave lateral tibial surface. Another ancillary study from OAI confirmed the importance of meniscus integrity and normal position93.

One limitation of paper III is that the study sample was relatively small (about 16% with missing data for the outcome), which led to wide confidence intervals for the effect estimates, though that did not change the interpretation of results. Another limitation is that BMLs are known to fluctuate considerably over time and only two time points’ BMLs were assessed. So it was not fully known of meniscus pathologies’ influence on these fluctuations.

### Arthroscopic partial meniscectomy and meniscus body extrusion

The included 223 subjects, have a mean (SD) age 59 (7.9) years, with both baseline and 18-month follow-up MRIs available and readable. Of these, 108 patients had been randomized to APM and 115 to standardized physical therapy.

The mean medial meniscus body extrusion at the baseline exam was similar; mean (SD) 3.2 (1.4) mm in the APM arm vs. 3.4 (1.5) mm in the physical therapy arm (p=0.34).

I found no statistically significant difference in the change of extrusion of the medial meniscal body over the 18 months follow-up period in the ITT analysis between the APM vs. physical therapy arm, +0.07 mm (95% CI -0.34, 0.49).

In the physical therapy arm, 42 patients (36.5%) crossed over to surgery during the 18 months of follow-up, and 4 patients (3.7%) randomized to APM never had the knee arthroscopy. I did not find any statistically significant differences in the change of medial body meniscal extrusion in the corresponding as-treated analysis -0.22 mm (95% CI -0.66, 0.22).

However, a major limitation is that in the trial it was not registered which compartment (medial or lateral) that was operated. Still, I expect most of the procedures to have been medial APMs (the most predominant procedure). The limitation have somewhat contributed to misclassification (non-differential) of exposure but is unlikely to have had a major impact on results.

###

### Cross-over between different groups

In paper IV, 42 patients, which comprise a substantial portion (36.5%) of the physical therapy arm, crossed over to APM during the 18 months follow-up period. Also 4 patients (3.7%) randomized to APM did not undergo the surgery. In non-blinded surgical trials, cross-overs remain an important problem, in particular if the patients (and the orthopaedic specialist) *a priori* have a preference for surgery. Interestingly, in the Finnish sham APM trial, published in New Engl J Med, where all subjects had knee arthroscopy, but only half of them had actual APMs, the cross-over was negligible146. The patients simply did not know if they had APM or not. The patient-relevant outcomes in the two treatment arms was virtually identical for pain, function as well as for so called mechanical symptoms168. Together, the two sham knee surgery trials so far have demonstrated the strong placebo effect of arthroscopic knee surgery, illustrating that the patients’ beliefs and expectations are critical components of the treatment effect146, 168.

### Intention to treat (ITT) analysis

ITT analysis is currently regarded as the gold standard for data analysis in RCTs. The advantages include the preservation of the randomization which minimizes the risk for confounding due to both known and unknown factors. However, when a lot of cross-over happen, the ITT analysis will not be an optimal choice to reflect the effect of the evaluated treatment per se149, 150. Thus, cross-overs in trials remain an important challenge and may be a major hurdle, especially to the ITT analysis, as it may potentially obscure differences in the outcomes of two treatments169, 170. In the present study results from ITT and as-treated analysis were similar, i.e. APM does not seem to influence meniscal position differently than non-surgical management

.

Table 9

The effect on incident/enlarging bone marrow lesions; results from random-effects mixed regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Medial compartment** |  | **Lateral compartment** |
|  | **Univariable** | **Multivariable** | **Multivariable (sensitivity)\*** |  | **Univariable** | **Multivariable** | **Multivariable (sensitivity)\*** |
| Number of knees |  | 672 | 668 |  |  | 675 | 671 |
| Number of persons |  | 342 | 345 |  |  | 342 | 345 |
| Meniscal extrusion (mm) | 1.40 (1.13, 1.75) | 1.24 (0.99, 1.57) | 1.27 (1.02, 1.59) |  | 1.66 (1.27, 2.17) | 1.69 (1.27, 2.25) | 1.70 (1.27, 2.26) |
| Age (years) | 1.10 (1.00, 1.20) | 1.11 (1.00, 1.22) | 1.10 (1.00, 1.22) |  | 0.96 (0.87, 1.07) | 0.95 (0.85, 1.06) | 0.95 (0.86, 1.06) |
| Body weight, per 5 kg increase | 1.14 (1.03, 1.27) | 1.15 (1.02, 1.30) | 1.17 (1.04, 1.32) |  | 1.08 (0.96, 1.20) | 1.10 (0.96, 1.26) | 1.10 (0.96, 1.25) |
| Body height | 1.00 (0.95, 1.04) | 0.99 (0.93, 1.05) | 0.99 (0.93, 1.05) |  | 1.01 (0.96, 1.06) | 0.96 (0.90, 1.03) | 0.96 (0.89, 1.02) |
| Physical activity | 0.99 (0.91, 1.07) | 0.99 (0.91, 1.07) | 1.00 (0.93, 1.08) |  | 1.02 (0.94, 1.11) | 1.01 (0.92, 1.10) | 1.01 (0.93, 1.10) |
| Ipsilateral meniscal damage | 1.97 (0.90, 4.35) | 1.45 (0.61, 3.44) | 1.51 (0.64, 3.53) |  | 2.08 (0.70, 6.19) | 1.59 (0.49, 5.14) | 1.58 (0.49, 5.06) |
| Tibial width (mm) | 1.01 (0.92, 1.12) | 0.96 (0.84, 1.09) | 0.95 (0.84, 1.07) |  | 1.01 (0.91, 1.12) | 1.02 (0.89, 1.17) | 1.03 (0.90, 1.18) |
| Valgus alignment | 0.73 (0.39, 1.34) | 0.85 (0.47, 1.56) |  |  | 1.47 (0.75, 2.88) | 1.47 (0.74, 2.92) |  |
| Knee injury | 0.94 (0.40, 2.20) |   | 0.77 (0.32, 1.86) |   | 1.26 (0.54, 2.91) |   | 0.93 (0.38,2.29) |

 \* In the sensitivity analysis adjusted for knee injury instead of valgus alignment (due to sparse data adjusting for both in one model was not feasible).

Table 10

The effect of arthroscopic partial meniscectomy (APM) vs. physical therapy on medial meniscus body extrusion over 18 months in patients with degenerative meniscus tear.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|   |   |  Intention-To-Treat |   |   |   | As Treated |   |
|  | APM |  Physical Therapy |   |  | APM | Physical Therapy |   |
|   | n=108 |  n=115 | *P-value* |   | n=146 | n=77 | *P-value* |
| Change in mm meniscal body extrusion (SD) | +0.47 (1.6) |  +0.40 (1.6) | *0.72* |   | +0.36(1.5) | +0.58(1.8) | *0.32* |

# Important limitations of the studies

All the MRI images from the three studied dataset were taken when patients were on a supine position. It is not known whether MRI images taken under weight-bearing conditions would yield different outcomes in my studies. A study using rotating MRI scanner shows that medial meniscal extrusion increase from the clinostatic to the orthostatic position171. Another study shows axial loading of knee has an effect on meniscus morphology159.

No study was done on anterior or posterior meniscus extrusion.

No investigations into the effects of different types' meniscal tear to meniscal extrusion as this could be much more complex and requires a much larger sample in order to ensure each type of tear has sufficient cases.

The two dimensional measurement methods is relatively easy compared with methods of meniscus segmentation.

Readers were not blind to sequences of images (Paper I, III, IV)

No registration on which side of meniscus was operated on (medial or lateral) in MeTeOR trial, I suppose most were on medial menisci as most of the procedures are performed due to medial meniscal tear.

# Clinical implications and considerations

Female gender, incident meniscal tear, and higher baseline value of extrusion are risk factors for increased meniscal body extrusion in subjects free of radiographic OA. That suggests why OA is more prevalent in middle aged women than in men. And those who have meniscal extrusion or meniscal tears found on MRIs should be careful for the faster progression towards knee joints’ degeneration. (Paper I)

Female gender is a significant risk factor for meniscal extrusion. Among females, those who are obese and have meniscal tear were found more meniscal extrusion on MRIs, thus more probable for the knee joints to deteriorate. So weight control is important for meniscus pathology and knee health. Meniscal extrusion may be a key event on the pathway between obesity and knee OA. (Paper II)

Meniscal extrusion and BMLs are both early features of knee OA. Meniscal body extrusion is an important factor influencing BML development/enlargement, and thus a potential treatment target in early knee OA. (Paper III)

Patients are usually suggested to undergo APM if their meniscal tears can not be repaired. However, paper IV suggested conservative treatment is an option. The similar effect would give instructions to both physicians and patients for the choices of treatment for meniscal repairs.

# Future perspectives

Future meniscal extrusion studies can include:

* Extrusions of anterior and posterior meniscal horns on sagittal MRI and see if they would yield similar outcome with coronal extrusions.
* Meniscal extrusion studies under weight- bearing conditions.
* The relations between meniscal extrusion and different type of meniscal tear. This would be much more complicated but an interesting study. A larger sample will be needed to ensure sufficient cases for each type of tears.
* Meniscal segmentation techniques can be used in future studies to increase precision and to provide more comprehensive information of changes in meniscal position.

# Summary

Meniscal extrusion is associated with meniscal tear, degeneration and even knee OA. MRI is an ideal tool to assess knee joints tissues and pathologies such as meniscal tears and extrusions. This thesis provides focus on the risk factors of meniscal extrusion as well its development and consequence, impact to other tissues and choices for clinical treatment.

Patients free of radiographic knee OA (n=340) would have enlarged meniscal extrusion over a 72 months period. Female gender, incident meniscal tear, and higher baseline value of extrusion are shown to be risk factors for increased meniscal body extrusion. The results suggest that meniscal extrusion may contribute to and mediate the well-known increase in knee OA incidence in middle-aged women.

Among overweight and obese women (n=395), ipsilateral meniscus tear and high BMI are factors associated with medial meniscus body extrusion based on my cross-section study of PROOF trial.

Base on the same baseline meniscal extrusion data, analysis for 18 month incident/enlargement bone marrow lesions show meniscal body extrusion is an important factor influencing BML development, and thus a potential treatment target in early knee OA. The influence is more profound in the lateral knee compartment.

Whether surgical or conservative method is more superior for treating meniscal pathologies is still in debate, investigation on meniscal body extrusion found APM in patients with OA does not differ significantly compared with the effect of non-operative management.

# **中文摘要**

半月板突出与半月板损伤，退变甚至膝关节骨关节炎都有关联。磁共振显像是用于评估膝关节组织及其病变，如半月板损伤及突出的一种理想工具。 这篇论著着眼于半月板突出的风险因素及其发展，后果，对于其它组织的影响以及临床处理的选择。

膝关节影像检查无骨关节炎的患者（n = 340）72个月后会有半月板突出程度增加。 女性， 偶发半月板损伤， 以及半月板基线高突出值被证实是半月板突出严重发展的风险因子。 本论著结果提示半月板突出可能会影响中年女性膝关节骨关节炎的高发率。

根据本文内的PROOF测试横向研究中，在超重肥胖女性中( n = 395), 同侧半月板损伤及高BMI （身高体重指数）为半月板体部突出的影响因素。

根据同一基线半月板突出数据， 分析18个月膝关节骨髓损伤发生/发展， 半月板体部突出为影响骨髓损伤发展的重要因素，因此也是在早期膝关节炎阶段的潜在治疗目标之一。 在膝关节外侧间室此影响更为显著。

手术治疗半月板病变是否优于保守治疗仍有争议， 基于半月板突出的研究发现关节镜下半月板部分切除术对于伴膝关节炎的患者与非手术处理的效果相比较并无明显差别。

# Summary of papers I-IV

#### Paper I: Risk factors for meniscal body extrusion on MRI in subjects free of radiographic knee osteoarthritis: longitudinal data from the Osteoarthritis Initiative

*Objective:* To determine risk factors associated with increased meniscal body extrusion on knee magnetic resonance (MR) images in subjects free of radiographic osteoarthritis (OA).

*Methods:* We selected 340 subjects (aged 45-55 years, mean [SD] body mass index 26.7 [4.4], 51% women) with Kellgren-Lawrence grade 0 in both knees and bilateral knee MR images available at the baseline, 24 months, 48 months, and 72 month exam from the Osteoarthritis Initiative (OAI). We assessed mid-coronal 3-T MR images from baseline through the 72-month exam. One observer measured widths of the tibia plateau and medial or lateral meniscal body extrusion for baseline and 72 months follow-up. Another observer assessed meniscal integrity at all four time points. We calculated an extrusion ratio ([meniscal body extrusion]/[tibia width] × 100) to account for knee size. We evaluated risk factors for increased meniscal body extrusion ratio from baseline to 72 months by a multivariable linear regression mixed model for medial and lateral compartment, respectively.

*Results:* In the medial compartment female sex (β = 0.35; 95% confidence interval [CI] 0.16-0.53), incident meniscal tear (β = 0.29; 95% CI 0.22-0.55), and the baseline value of the extrusion ratio (β = 0.63; 95% CI 0.56-0.70) were associated with increased extrusion ratio by 72 months. Results were similar for the lateral compartment.

*Conclusion:* Only female sex, incident meniscal tear, and higher baseline value of extrusion are risk factors for increased meniscal body extrusion in subjects free of radiographic OA. The results suggest that meniscal extrusion may contribute to and mediate the well-known increase in knee OA incidence in middle-aged women.

#### Paper II: Factors associated with meniscal body extrusion on knee MRI in overweight and obese women

*Objective:* To determine factors associated with higher degree of meniscal body extrusion in overweight and obese women at high risk of knee osteoarthritis (OA).

 *Design:* We used baseline data of the PROOF study, Netherlands, comprising overweight or obese women aged 50 to 60 years, free of clinical knee OA. All subjects completed a questionnaire on knee complaints and physical activity, underwent physical examination, radiography, and 1.5 Tesla MRI of both knees. Using the mid-coronal MRI slice, one blinded observer measured tibial plateau width and meniscal body extrusion of both menisci in both knees. The association between baseline factors and meniscal extrusion, were analyzed with a random effects regression model. In addition, we used a fixed effect regression model for evaluation of knee-specific factors.

*Results:* Mean age of the included women (n=395) was 55.7 years and mean body mass index 32.4 kg/m2. Of all knees, 23% had an absolute medial meniscus body extrusion ≥3.0 mm and 4% had lateral meniscus body extrusion ≥3.0 mm. In the multivariable model, the medial meniscus extrusion was increased by 0.44 mm (95% confidence interval [CI] 0.11, 0.77) when a medial meniscus tear was present, by 0.20 mm per 5 kg/m2 (95% CI 0.05, 0.35) increase in body mass index and by 0.25 in the presence of mild knee symptoms (95% CI 0.05 to 0.44). Kellgren-Lawrence grade ≥1 and tibia width were associated with increased both medial and lateral extrusion.

*Conclusion:* In women, ipsilateral meniscus tear and high body mass index are factors associated with medial meniscus body extrusion.

#### Paper III: The association between meniscal body extrusion and the development of bone marrow lesions on knee MRI in overweight and obese women

*Objective:* To determine the association between meniscal body extrusion and bone marrow lesion (BML) development/enlargement in overweight and obese women at high risk of knee osteoarthritis (OA).

*Methods:*We used baseline and 30 months follow-up data of the PROOF study, Netherlands, comprising overweight or obese women aged 50 to 60 years, free of clinical knee OA. All subjects completed a questionnaire on knee complaints and physical activity, underwent physical examination, radiography, and repeated 1.5 Tesla MRI of both knees. Using the mid-coronal MRI slice, one observer measured tibial plateau width and meniscal body extrusion of both menisci in both knees. BMLs and meniscal damage were read using the semi-quantitative MOAKS scoring system by another observer. The association between BML development and meniscal extrusion was primarily analyzed with a random-effects logistic regression model adjusted for age, body weight, body height, physical activity, meniscus damage, knee alignment, and tibia width. In addition, we used a fixed-effect regression model for evaluation of knee-specific factors.

*Results:*In our primary model, there was about 24% increased risk of BML incidence/enlargement per 1 mm extrusion (95% confidence interval [CI] 0.99, 1.57) for medial compartments and 69% risk increase (95% confidence interval [CI] 1.27, 2.25) for the lateral compartments. Results from the fixed-effects regression model were similar, strengthening the validity of the findings.

*Conclusions:*Meniscal body extrusion is an important factor influencing BML development/enlargement, and thus a potential treatment target in early knee OA.

#### Paper IV: The Effect of Arthroscopic Partial Meniscectomy in Patients with Osteoarthritis on Meniscal Body Extrusion

Purpose: Meniscal damage and extrusion are both strongly associated with the progression of knee OA. Concerns have recently been raised that arthroscopic partial meniscectomy (APM) may accelerate OA development. It is currently unclear whether performing APM or leaving a meniscal tear in situ affect meniscus position differently. Thus we determined the effect of APM on medial meniscal body extrusion in patients with OA and meniscal tear.

Methods: Post-hoc analysis using data from the MeTeOR trial (ClinicalTrials.gov number, NCT00597012), a multi-center randomized controlled trial that involved patients aged 45 or older with knee symptoms and meniscal tear as well as osteoarthritic changes detected on MRI (cartilage lesions) or radiography. Patients were randomized to either APM coupled with postoperative physical therapy (PT) or a standardized PT regime. Cross-over from PT to APM due to treatment failure was allowed. One orthopedic surgeon, who was blinded to treatment allocation, actual treatment received, and patient characteristics, but who had knowledge of the time sequence, performed paired meniscal measures on the baseline and 18-month mid-coronal 1.5T knee MR images. The observer measured medial meniscal body extrusion to the closest 0.1 mm using Sante DICOM Editor software. Intraobserver reliability (intra-class correlation coefficient) was 0.85 (95% CI: 0.73-0.92). We defined our primary outcome as the absolute change in mm of the position of the external medial meniscal body margin from baseline to the 18-month exam. We used the intention-to-treat (ITT) principle for the primary analysis, and we also performed a secondary as-treated analysis, i.e., taking into account the cross over after randomization (including those who crossed over from PT to APM into the APM group).

Results: The MeTeOR trial patients have mean (SD) age 59 (7.9) years at baseline and 56% were women. In this analysis we included the first 223 patients who had both baseline and 18-month follow-up knee MRIs available and readable. Of these, 108 patients were randomized to APM and 115 to standardized PT. The mean medial meniscus body extrusion at the baseline exam was similar; mean (SD) 3.2 (1.4) mm in the APM arm vs. 3.4 (1.5) mm in the physical therapy arm (p=0.34). We found no statistically significant difference in the change of extrusion of the medial meniscal body in the ITT analysis; mean (SD) change +0.47 mm (1.6) in the APM arm vs +0.40 (1.6) mm in the PT arm (p=0.72). In the PT arm, 42 patients (36.5%) crossed over to surgery during the 18 months of followup, and 4 patients (3.7%) randomized to APM never had the surgery. We did not find statistically significant differences in the corresponding as-treated analysis, mean (SD) change +0.36 mm (1.5) in those having APM (n=146) vs +0.58 (1.8) mm in those patients having PT only (n=77) (p=0.32).

Conclusion: We observed on average small changes in medial meniscal body extrusion over 18 months in MeTeOR trial participants. APM of a meniscal tear in patients with knee OA does not lead to increased meniscal body extrusion as compared to non-operative management.

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