Meniscal Tear - A Feature of Osteoarthritis

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Abstract

Meniscectomy is recognized as an important risk factor for the development of knee osteoarthritis (OA), a disease that traditionally has been considered as a simple "wear and tear" phenomenon. However, despite numerous reports, little evidence has been presented that a limited meniscal resection, compared with a more extensive resection, reduces the risk of OA by preserving meniscal function. *Why?* This thesis provides one possible answer to that question.

Patients, who had undergone isolated meniscal resection in 1973, 1978, or between 1983 and 1985 at Lund University Hospital, Sweden, were reviewed clinically and radiographically 15–22 years after the surgical procedure.

Of the subjects (n = 317) almost 50% had developed radiographic OA in their operated knee, but just over half of these patients were symptomatic. An additional 20% of the patients had knee symptoms, but did not have radiographic knee OA. These results confirm a limited correlation between radiographic features of the disorder and symptoms.

A degenerative type of meniscal tear and obesity were the factors most strongly associated with both radiographic knee OA and symptomatic radiographic knee OA.

Partial meniscal resection induced less radiographic changes related to knee OA compared with total meniscectomy, but the patient-relevant outcomes remained essentially the same.

If radiographic hand OA was present there was an increased likelihood of the patient also having knee OA following meniscectomy. This finding was independent of age, and therefore an inherited susceptibility to the disease contributes to the risk of knee OA after meniscal tear. Genetic and environmental risk factors interact in OA development.

A degenerative meniscal lesion is often associated with early-stage knee OA, a disorder also involving the meniscal tissue. The tear may thus represent the first "signal" feature of OA. The challenge for the health professional is to discriminate between symptoms caused by a meniscal tear and those caused by OA. Meniscal resection may not benefit the patient with early-stage knee OA. The intervention merely removes evidence of the disorder, while the OA joint degradation proceeds.

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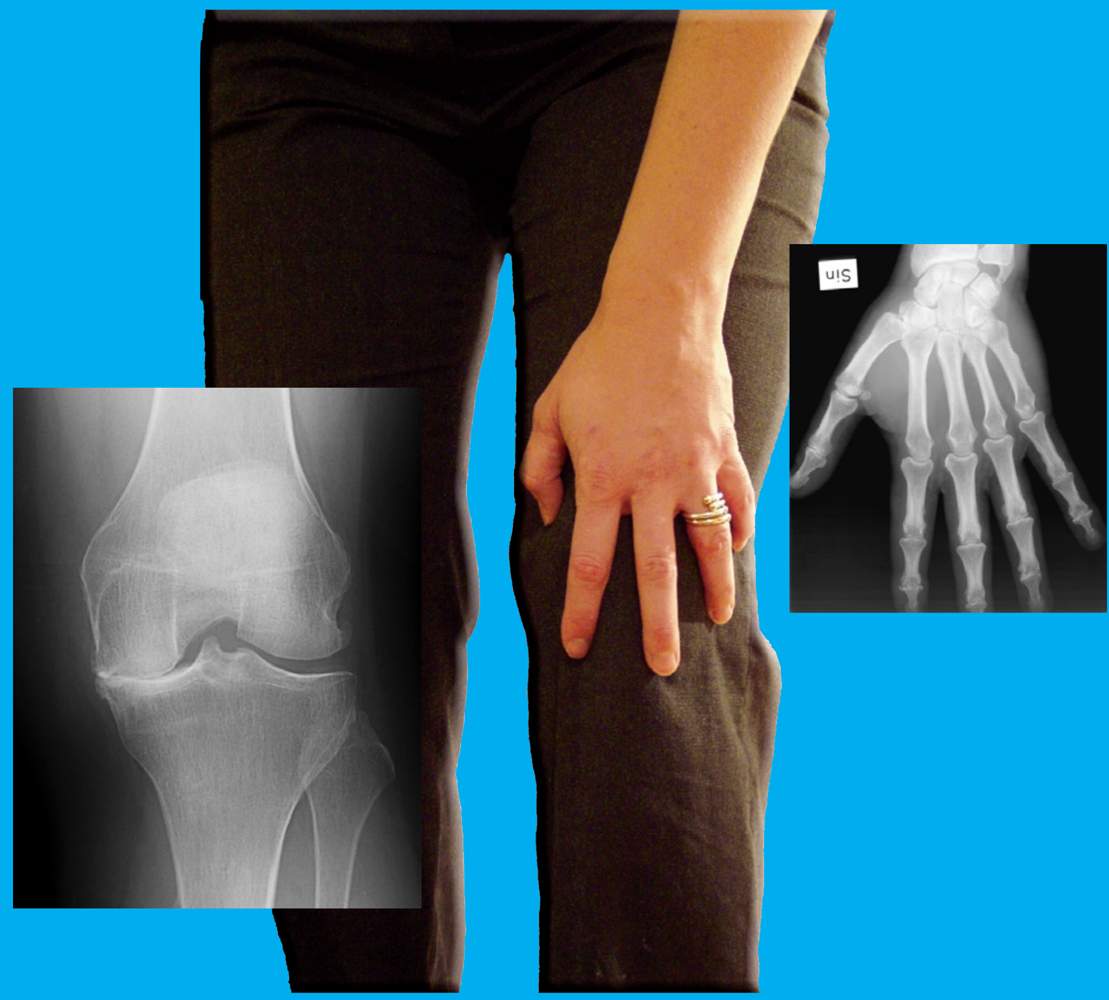

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Cover images: Photo by Martin Englund illustrating knee pain, and radiographs from the study material showing knee and hand osteoarthritis, respectively.

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List of papers

I. Englund M, Roos E M, Roos H P, Lohmander L S. Patient-relevant outcomes fourteen years after meniscectomy: influence of type of meniscal tear and size of resection. Rheumatology (Oxford) 2001; 40 (6): 631-9.

II. Englund M, Roos E M, Lohmander L S. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum 2003; 48 (8): 2178-87.

III. Englund M, Paradowski P T, Lohmander L S. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. Arthritis Rheum 2004; 50 (2): 469-75.

IV. Englund M, Lohmander L S. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Manuscript submitted for publication.

Thesis at a glance

Paper	Question	Patients	Year of meniscectomy	Follow-up time (range years)	Outcomes	Answer
I	Does the clincal outcome differ depending on type of meniscal tear and size of a limited meniscal resection?	205	1983–1985	12–15	KOOS, SF-36	Yes, a degenerative meniscal tear is associated with worse clinical outcome than a traumatic tear. I suggest that a degenerative meniscal tear may indicate early-stage knee OA.
II	Does the risk of developing knee OA differ depending on type of meniscal tear and extent of a limited meniscal resection?	155 + 68 controls	1983–1985	15–18	KOOS, knee radiographs	Yes, factors associated with a higher risk of knee OA are degenerative meniscal lesions, and to a lesser extent the size of the meniscal resection.
III	Is there an association between hand OA (hereditary) and OA of the knee after meniscectomy?	170	1973 or 1978	17–22	Knee and hand radiographs	Yes, having hand OA is associated with an increased likelihood of having knee OA after meniscectomy. Postmeniscectomy OA is not secondary OA only.
IV	What are the major prognostic factors for knee OA after meniscal resection?	317 + 68 controls	1973, 1978, or 1983–1985	15–22	KOOS, knee radiographs	Local biomechanical and systemic factors interact in the development of knee OA after meniscal resection. Major factors that are associated with poor outcome are obesity, a degenerative type of meniscal tear, total meniscectomy, and female sex.

KOOS = Knee injury and Osteoarthritis Outcome Score,
SF-36 = Short-Form 36-item Health Survey,
OA = osteoarthritis.

Description of contribution

Paper I

Study design:	Martin Englund Ewa Roos Harald Roos Stefan Lohmander
Data collection:	Martin Englund Harald Roos
Data analysis:	Martin Englund
Manuscript writing:	Martin Englund
Manuscript revision:	Ewa Roos Harald Roos Stefan Lohmander

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Paper IV

Study design:	Martin Englund Stefan Lohmander
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Data analysis:	Martin Englund
Manuscript writing:	Martin Englund
Manuscript revision:	Stefan Lohmander

Definitions and abbreviations

95% CI	95% confidence interval
ANOVA	Analysis of variance
BMI	Body mass index
CMC 1	First carpometacarpal
DIP	Distal interphalangeal
Generalized OA	Osteoarthritis in which systemic (genetic) predisposition is more important than local (mechanical) factors
IP	Interphalangeal
JSN	Joint space narrowing
K/L	Kellgren and Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score
MRI	Magnetic resonance imaging
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	Odds ratio
Outcome	Something that follows as a result
Patient-relevant outcome	Outcome based on the patient's experiences, preferences and values
PIP	Proximal interphalangeal
Primary OA	Osteoarthritis without known cause
Secondary OA	Osteoarthritis with a known cause
SF-36	Short-Form 36-item Health Survey
WOMAC	Western Ontario and MacMaster Universities Osteoarthritis Index

Introduction

OA—the most common cause of musculoskeletal disability

Osteoarthritis (degenerative arthritis, osteoarthrosis, artrosis, OA) is a slowly progressive joint disease, which may lead to local destruction of the joint. Pain, limitation of movement, and tenderness are the most common symptoms, which often lead to severe disability. Among the most frequent joints affected by OA are the knee, the hip, the cervical spine, and the distal interphalangeal joints and the base of the thumb of the hands.

OA is the most common cause of musculoskeletal disability in developed countries, and is now listed among the top 10 of the global disease burden according to the World Health Organization (Murray and Lopez 1996). In the United States approximately 6% of the population 30 years of age or older, and 12% of those 65 years of age or older, suffer from symptomatic knee OA (Felson and Zhang 1998). The prevalence of the disorder increases drastically with age, and the proportion of elderly in the society continues to increase. Therefore, OA will cause the society increasing socio-economic costs, which already today are tremendous.

Treatment for OA is mostly symptomatic, but efforts are made to develop drugs that may slow or halt the progression of OA. The disease is the main cause of joint replacement surgery, even though a relatively small percentage of patients deteriorate so much that surgical intervention is required (Dieppe 1999).

OA—a syndrome of 'joint failure'

For many years OA has been regarded as a simple degenerative "wear and tear" phenomenon. However, in the last decades there has been a major shift in the view of the disorder. OA is not a homogeneous disease, it is a rather complex syndrome with a common end-stage of "joint failure". Therefore, there are several difficulties in defining the disorder (Figure 1).

Pathologically, loss of joint cartilage, formation of osteophytes, sclerosis of subchondral bone, subchondral cysts, and synovial inflammation characterize OA. In clinical practice, the most widely used definitions include morphological changes, as well as clinical features. When the disease is visualized by conventional radiographic examination, the OA has progressed so far that the joint cartilage has sustained irreversible damage (Figure 2).

Accordingly, one of the areas of attention in OA research is to detect early alterations in joint metabolism by molecular markers (Lohmander and Poole 2003). In addition, various modern imaging techniques, such as magnetic resonance imaging (MRI), have the potential to detect very early structural change (Peterfy 2003). MRI is rapidly becoming more accessible. However, there is still a lack of validated criteria to define OA. Therefore, in addition to cost and practical aspects, MRI has only recently become useful in the study of OA in larger populations or clinical practice.

Knee OA—several risk factors

OA is a heterogeneous disorder and accordingly there are several factors associated with the disease. The major risk factors for knee OA can be

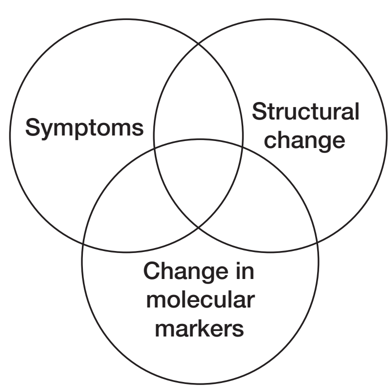

Figure 1. Current and future tools in defining OA.

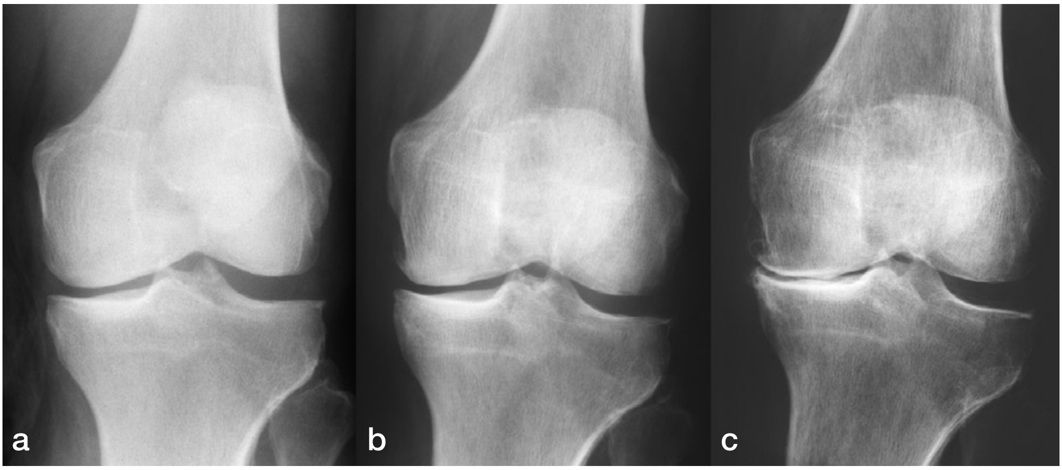

Figure 2. Radiographic progression of knee osteoarthritis. The radiographs are obtained 7 years (a), 13 years (b), and 21 years (c) after meniscectomy, respectively. Typical features as joint space narrowing, marginal osteophytes, and sclerosis are developing.

categorized as systemic or local biomechanical factors.

Systemic risk factors

Knee OA, as well as most forms of OA, appears to be strongly genetically determined (Spector et al. 1996, Loughlin et al. 2002). It is likely that most genes affecting OA will affect disease occurrence in many joints, although there may be specific genes for specific joints. So far, most candidate genes identified involve hand or hip OA (Leppavuori et al. 1999, Ingvarsson et al. 2001, Demissie et al. 2002, Stefansson et al. 2003). Ongoing research will no doubt identify additional loci, genes, and genetic variations associated with knee OA (Spector and MacGregor 2004).

Knee OA is less common in younger individuals, but highly prevalent in the older population. The incidence increases greatly after the age of 50. This epidemiological pattern may partly be explained by the fact that it takes several years to develop the typical radiographic features of OA that are normally required to define the disorder. The start of the osteoarthritic disease process occurs at an age much earlier.

Women are more prone to develop knee OA than are men. It is not clear why, but hormonal factors may play a role (van Saase et al. 1989, Felson et al. 1997b, Zhang et al. 1998).

Evidence suggests an inverse relationship between knee OA and osteoporosis, i.e., high bone density is a risk factor (Sowers et al. 1999, Zhang et al. 2000).

Local biomechanical risk factors

Prospective studies have confirmed knee trauma to be a significant risk factor for development of knee OA (Gelber et al. 2000, Wilder et al. 2002). Injury to the anterior cruciate ligament, isolated or with associated injuries to the menisci or collateral ligaments, leads to a high frequency of radiographic knee OA (Neyret et al. 1993, Roos et al. 1995). Among subjects who have undergone total meniscectomy, with no other associated injuries, approximately 50% have radiographic knee OA about 20 years after the surgery (Roos H. et al. 1998). Twenty years may be regarded as a long time interval, but considering that traumatic injury normally occurs in young adults, radiographic knee OA may thus already be present at 35–40 years of age. It is not yet established how quickly the radiographic changes appear after a major joint injury. Recent findings using MRI suggest that significant rates of cartilage loss appear already within a couple of years after meniscal resection (Cicuttini et al. 2002).

In epidemiological studies, heavy physical activity is associated with a higher risk of developing knee OA (Anderson and Felson 1988, Felson et al. 1997b, McAlindon et al. 1999, Cheng et al. 2000). This may be due to a higher risk of joint injury in highly active individuals. However, excessive repetitive joint use appears to be associated with OA as well.

Obesity is well established as a risk factor for the development of knee OA, but why obesity causes OA is not entirely clear (Felson et al. 1988, Spector et al. 1994, Hochberg et al. 1995, Felson et al. 1997b, Gelber et al. 1999). Increased joint loading in obese individuals may not be the only explanation.

Joint deformity, knee malalignment, laxity, reduced proprioception, altered gait pattern, and quadriceps muscle weakness are other factors that are associated with OA of the knee (Sharma et al. 1997, 1998, 2003).

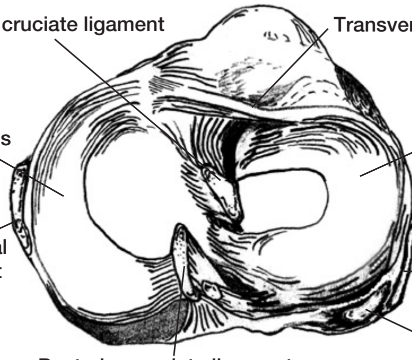

Figure 3. Anatomy of the menisci. Redrawn and modified from Warren R F, Arnoczky S P and Wickiewicz T L. Anatomy of the knee. In: The lower extremity and spine in sports medicine. (Eds. Nicholas J A, Hershman E B). CV Mosby Co, St. Louis 1986; 657–94.

The meniscus—gross anatomy

The menisci are two semi-circular fibrocartilaginous structures in the knee that are located between the medial and lateral articular surfaces of the femur and tibia. In cross-section, the meniscus is wedge-shaped with a thick peripheral convex base attached to the joint capsule. The surface facing the tibia is flat and the femoral surface is concave. Both menisci are attached to the tibia through the anterior and posterior horns, where circumferential meniscal matrix fibers continue as ligaments attached to the intercondylar bone. The lateral meniscus has more central attachments to the intercondylar area than the medial meniscus. Furthermore, the medial meniscus is firmly attached to the medial collateral ligament, whereas the lateral meniscus is separated from the lateral collateral ligament and the joint capsule at the popliteal hiatus. The arrangement makes the lateral meniscus more mobile than the medial meniscus (Figure 3).

Branches from the medial, lateral, and middle genicular arteries account for most of the blood supply to the menisci. The peripheral border is infiltrated by capillaries that penetrate 10–30% of the meniscus width (Arnoczky and Warren 1982, Day et al. 1985).

A branch from the tibial nerve, the posterior articular nerve, innervates the peripheral part of the meniscal tissue. The nerve fibers mostly follow the blood vessels, with the two horns of the meniscus being the richest innervated. The inner 2/3 of the meniscus have no nerves (Wilson et al. 1969, Day et al. 1985, Mine et al. 2000).

The meniscus—biochemical composition and structure

The sparse meniscal population of fibrochondrocytes synthesizes the meniscal matrix. The major matrix components are water, collagen, and proteoglycans. In contrast to articular cartilage, which contains principally type II collagen, meniscal collagen is mainly type I. The tightly woven collagen fibers are predominantly arranged in a circumferential pattern, but there are also radial, perforating, and some superficial fibers oriented in a more random pattern. The proteoglycans are large hydrophilic molecules that are woven into the collagen meshwork and can entrain water 50 times their weight. The meniscus contains considerably less proteoglycan than articular cartilage (Fithian et al. 1990).

Meniscal function—load transmission and shock absorption

The most important property of the collagen-proteoglycan meniscal matrix is its ability to resist tension, compression, and shear stresses. The main functions are load transmission and shock absorption during dynamic movements (Walker and Erkman 1975, Shrive et al. 1978, Seedhom and Hargreaves 1979, Fukubayashi and Kurosawa 1980, Kurosawa et al. 1980). The menisci distribute stress over a large area of the articular cartilage. When the knee is loaded, the tensile strength of the meniscal matrix (hoop tension) counteracts extrusion of the meniscus. Therefore, the healthy meniscus mainly responds to load with compression.

The meniscus has also been suggested to assist in joint stability, lubrication, and proprioception (Markolf et al. 1981, Levy et al. 1982, Shoemaker and Markolf 1986, Zimny et al. 1988, Levy et al. 1989, Assimakopoulos et al. 1992).

Meniscal tears—often not traumatic

Two major categories of meniscal injuries are described, traumatic and gradual degeneration with aging (Smillie 1962, Noble and Hamblen 1975, Poehling et al. 1990).

Traumatic lesions normally occur in younger sports-active individuals, with or without associated cruciate ligament injury. The meniscal tear is commonly due to internal rotation of the femur as the flexed knee moves toward an extended position. The meniscus usually splits in a longitudinal direction. The central part of the meniscus may dislocate centrally and cause locking of the knee. Traumatic injury is considered more frequent in the medial meniscus, mainly due to its lower mobility, larger diameter, and thinner periphery (Brantigan and Voshell 1941).

Degenerative tears, described as horizontal cleavages, or flap or complex tears (Figure 4) are associated with an older age group (Smillie 1962, Poehling et al. 1990). These tears are common. In asymptomatic subjects with a mean age of 65 years, a tear was found in 67% using MRI, whereas in patients with symptomatic knee OA, a meniscal tear was found in 91% (Bhattacharyya et al. 2003). Similar findings have previously been made in random necropsy cases, where 60% of the subjects had a horizontal cleavage lesion (Noble and Hamblen 1975).

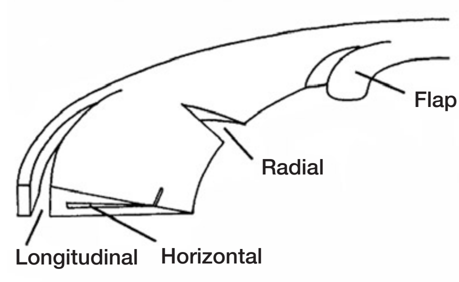

Figure 4. **Classification of meniscal tears**

Longitudinal tear: A vertical tear in the meniscus with a longitudinal direction. Usually located in the periphery of the meniscus. The longer the tear the more unstable it is, and the end result is the dislocated central part of the meniscus—bucket-handle tear.

Horizontal tear: A horizontal cleavage in the meniscal tissue.

Radial tear: A vertical tear starting in the free (central) margin of the meniscal tissue.

Flap tear: An oblique vertical cleavage causing a flap tear (parrot beak). A flap tear could also be caused by a horizontal tear.

Tear in degenerative meniscus: A tear or multiple tears in a degeneratively changed meniscal tissue (not shown in figure).

Surgical treatment of meniscal tears—a history of firm beliefs

Meniscal repair

The first report known of a meniscal surgical procedure was a procedure of meniscal repair. In 1883 a British surgeon, Thomas Annandale, successfully sutured a torn anterior horn of a medial meniscus (Annandale 1885). Encouraged by the good result, he expressed the opinion that "this, or some similar proceeding, may now become an established means of treatment, when the more simple methods fail to give relief". However, 4 years later, he published another report, where he justified total excision of the meniscus rather than suture, and that view would prevail for over 80 years (Annandale 1889).

Today, techniques of meniscal repair are widely used when the lesion is located within or adjacent to the vascularized zone of the meniscus. However, rehabilitation after repair is more extensive than after meniscal resection, and the long-term outcome of meniscal repair compared with meniscectomy with respect to OA is still unknown (Stone et al. 1990, DeHaven et al. 1995, Rockborn and Messner 2000, Steenbrugge et al. 2002).

Total meniscectomy

One of the early published reports of short-term results after total meniscectomy concluded that most patients had good results (Mitchiner 1922). Nine years later, another investigator reported that although about 80% of the patients were satisfied with their result, only about half of these were truly symptom free. Poor results correlated with the presence of OA before meniscectomy (MacAusland 1931).

In the mid 1930s King reported on degenerative changes after meniscectomy in dogs (King 1936b), and that a detachment of the meniscus from the periphery might heal, thanks to its vascular supply (King 1936a). He therefore suggested that surgeons should consider meniscal repair instead of total excision. However, there was little notice taken of the urging from King at the time.

Patients (n = 144) who had undergone total meniscal extirpation between 1929 and 1938 at the Department of Orthopedics in Lund, Sweden, were reexamined with a mean follow-up time of 6 years (Sjövall 1942). The author concluded that there was no increased frequency of early post-operative *arthrosis deformans* and the overall clinical outcome was considered good. The average hospital stay was 1 month. The following year, another Swedish report of total meniscectomy was published, this time with a follow-up time of 5 to 25 years (Lagergren 1943). In addition to pointing out the increasing number of patients with OA with the length of the observation period, the author made another interesting conclusion, "secondary arthrosis deformans as a sequela of a meniscal operation is essentially more frequent in women than men". His finding of female sex as a risk factor for knee OA is still an area of great attention in epidemiological research.

In the late 1940s, the first widely quoted report of frequent radiographic changes after meniscectomy was published (Fairbank 1948). He speculated that the changes were due to the loss of the load-protective function of the menisci, resulting in remodeling of the joint. Fairbank concluded: "Meniscectomy is not wholly innocuous; it interferes, at least temporarily, with the mechanisms of the joint." However, there was still a firm belief in the orthopedic community that the menisci were a rather troublesome tissue, and their removal was therefore considered a benign procedure for at least another 20 years.

From the late 1960s to the 1980s there are an increasing number of follow-up reports of total meniscectomy published, and they all indicate a high frequency of radiographic changes and reduced knee function (Gear 1967, Jackson 1968, Tapper and Hoover 1969, Appel 1970, Johnson et al. 1974, Noble 1975, Noble and Erat 1980, Sonne-Holm et al. 1980, Lotke et al. 1981, Doherty et al. 1983, Allen et al. 1984, Jørgensen et al. 1987). However, the actual increase in risk of OA after total meniscectomy was for long unknown. Not until the late 1990s, a study from my department showed a 6-fold increase in the risk of radiographic OA 21 years after total meniscectomy compared with controls matched for age and sex (Roos H. et al. 1998).

Partial meniscectomy

Already in 1947 Lipscomb and Henderson reported that partial meniscectomy produced equally good results in the short term, and therefore suggested this to be an alternative to total excision (Lipscomb and Henderson 1947). However, there was a strong conviction that total excision was necessary to produce regeneration of meniscal tissue and good results (Smillie 1944).

Not until about 20 years later, Tapper and Hoover indicated that leaving the peripheral rim intact produced better long-term results in the treatment of bucket-handle (longitudinal) tears (Tapper and Hoover 1969), and when the arthroscopic technique was introduced during the 1970s interest increased in excising only the damaged portion of the meniscus. In the same period of time, several biomechanical studies reported on the load bearing and shock absorbing functions of the menisci (Walker and Erkman 1975, Shrive et al. 1978, Seedhom and Hargreaves 1979, Fukubayashi and Kurosawa 1980, Kurosawa et al. 1980). It was now time to shift the paradigm to a more restrained attitude to total meniscectomy, 80 years after the introduction of the procedure.

There are evident short-term benefits of the arthroscopic technique of surgery and partial meniscal resection in terms of length of hospital stay and rehabilitation (McGinity et al. 1977, Dandy 1978, Guhl 1979, Oretorp and Gillquist

1979). However, despite numerous follow-up reports, the evidence of an improved long-term outcome is still limited compared with total extirpation (Faunø and Nielsen 1992, Neyret et al. 1993, Burks et al. 1997, Higuchi et al. 2000, Andersson-Molina et al. 2002). The only prospective study failed to detect significant benefit with respect to radiographic changes of partial compared with total meniscectomy (Hede et al. 1992a). It seems that the use of a surgical technique that is supposed to preserve meniscal function does not substantially reduce the incidence of knee OA. *Why?* This thesis provides one possible answer to that question.

Aims of the study

General aim

To enhance the knowledge of the long-term radiographic and patient-relevant outcome after meniscal tear and resection, and to identify major risk factors for the development of knee OA after meniscectomy.

Specific aims

- To assess the patient-relevant outcome with respect to type of meniscal tear and extent of surgical resection (Paper I).
- To evaluate the patient-relevant and radiographic outcome with respect to type of meniscal tear and extent of surgical resection (Paper II, IV).
- To estimate the relative risks of developing knee OA, with respect to type of meniscal tear and extent of surgical resection using nonoperated control subjects (Paper II).
- To examine the influence of a hereditary form of OA, i.e., the presence of primary radiographic hand OA, on radiographic knee OA after meniscectomy (Paper III).
- To investigate the influence of age, sex, obesity, knee-load, surgical technique, operated compartment, and peroperative cartilage changes on the patient-relevant and radiographic outcome after meniscal resection (Paper IV).
- To investigate the relationship between radiographic knee OA and self-reported symptoms (Paper II and IV).

Subjects and methods

Ethical considerations

The ethics committee of the Faculty of Medicine, Lund University approved the studies. Informed consent was obtained from all participating subjects.

Patients—well-characterized study cohorts

Patients, who in 1973, 1978, or between 1983 and 1985 had undergone isolated meniscal resection at Lund University Hospital, Sweden, were identified retrospectively through the surgical code system or by manual search of the surgical records. Surgical findings and other knee relevant information were retrieved from the hospital records. The classification of the meniscal tears was modified after previously described criteria (Newman et al. 1993). I additionally classified horizontal, complex, and flap tears, and tears in a meniscus with degenerative changes as degenerative meniscal tears, according to findings in epidemiological (Poehling et al. 1990) and necropsy studies (Noble and Hamblen 1975, Noble 1977). Cases where consensus could not be reached during data extraction were noted as unclassified. Joint cartilage changes recorded at the time of surgery were graded as no changes, lesions without visible bone, or as exposed bone. When there was no report of cartilage status, the cartilage was regarded as normal. If any part of the meniscus was removed, leaving a minimum of 2/3 of the meniscal surface intact, I classified the resection as partial. I considered a resection of more than 1/3 of the meniscal surface but still leaving intact meniscal tissue, commonly a peripheral rim, as subtotal. A total meniscal extirpation, which is carried out along the transitional zone between the meniscus and the joint capsule, was recorded as a total meniscectomy.

General exclusion criteria from the study were: being under 10 years of age at the time of index surgery, a report of death, relocation outside the South Swedish Health-care region, or a diagnosis of rheumatoid-, crystal- or psoriatic arthritis. Knee-specific criteria for exclusion (either knee) were: previous knee surgery, major ligament injury before or at the time of assessment, meniscectomy in both compartments of the same knee, osteochondritis dissecans, fracture in or adjacent to the knee, septic arthritis, osteonecrosis, or radiographic changes indicating knee OA at the time of index surgery. In the cohort of patients operated between 1983 and 1985, 6 patients with hip arthroplasty and 4 subjects with severe neurological or muscular disease were also excluded as a consequence of the primary objective when identifying that cohort (Paper I). Current addresses were obtained from the National Population records. Patients were invited to clinical and radiographic assessment in 1994, 1995, or in 2000, respectively. Demographic data of study cohorts and the primary outcomes used are shown (Table 1).

When I evaluated the association between radiographic hand OA and radiographic knee OA in the patients operated in 1973 or 1978 (Paper III), patients who had undergone meniscectomy in both compartments (n = 1), or had had previous knee surgery in the contralateral knee (n = 9), were included.

In present study, the loss of 30% to radiographic assessment is low compared with other reports of clinical and radiographic long-term outcome of meniscectomy. However, to exclude possible inclusion bias, I evaluated the candidate risk factors of nonparticipants and subjects without knee radiographs of the largest of the cohorts (the patients operated between 1983 and 1985). There were no significant differences with respect to sex, operated compartment, type of surgical technique, extent of meniscal resection, or type of meniscal tear, but compared with the participants, the mean age of the nonparticipants was 6 years younger at index surgery (Paper II). Furthermore, the subjects who participated in the mailed survey in 1998 (Paper I), but did not participate in the clinical and radiographic assessment in 2000, had similar

Table 1. Number and main characteristics of the patients and control subjects included in Paper I–IV, and the outcome measures used

Paper	N	Year of meniscectomy	Men, no. (%)	Age at assessment, mean (range) years	Time since surgery, mean (range) years	Outcomes
I	205	1983–1985	160 (78)	50 (27–83)	14 (12–15)	SF-36, KOOS
II	155	1983–1985	128 (83)	54 (30–85)	16 (15–18)	KOOS, knee radiographs
III	170	1973 or 1978	131 (77)	54 (33–87)	20 (17–22)	Knee and hand radiographs
IV	317	1973, 1978, or 1983-85	251 (79)	54 (30–87)	18 (15–22)	KOOS, knee radiographs
II, IV	68	Control subjects	50 (74)	56 (37–79)	–	KOOS, knee radiographs

SF-36 = Short-Form 36-item Health Survey, KOOS = Knee injury and Osteoarthritis Outcome Score.

self-reported outcome compared to the participants. This finding indicates little or no inclusion bias with respect to symptoms from that stage, but naturally I do not know anything about the symptoms of subjects who declined any form of participation.

Control subjects—are needed

To evaluate and compare the outcome of the patients, I needed an appropriate reference group. The use of the contralateral knee as a reference is inappropriate since this knee displays changes in cartilage metabolism after joint injury (Dahlberg et al. 1994) and develops frequent radiographic changes (Allen et al. 1984, Faunø and Nielsen 1992). There may be several explanations. First, the contralateral knee may have been subjected to trauma in absence of report. Second, an injury in one knee may change the joint loading and gait patterns, leading to an overload of the contralateral knee (Shakoor et al. 2002). Third, injury and synovitis in one knee may increase the risk of arthritic changes in the contralateral knee through neurogenic mechanisms (Decaris et al. 1999). Fourth, an increased prevalence of radiographic OA in the contralateral knee may reflect an endogenous (hereditary) increased risk of OA in some individuals (Doherty et al. 1983). An additional argument for using control subjects is that there may be difficulty for the patient to discriminate between knees when answering questions, especially about knee function and knee-related quality of life.

The reference group used in present work (Paper II and IV) was identified in conjunction with previous studies from my department (Roos H. et al. 1998, Roos et al. 1999). The size of the group was based on the assumption that the risk of developing radiographic OA in the index knee after meniscectomy was at least 4.5 times higher than controls. Sixty individuals were then needed in order to provide a statistical power of 83% at 5% significance level. To ensure this number 2 age- and sex-matched control subjects for each of the patients operated in 1973 were identified using National Population Records matching zip code. Of the designated control subjects 83 did not want to answer the questionnaire or undergo radiographic or clinical examination, 16 were excluded due to previous meniscectomy or known cruciate ligament injury, and 40 subjects were excluded because they represented a "double control", i.e., another control subject was already matched with that particular patient. Of the remaining 75 subjects, 6 did not show up at examination despite their acceptance to participate, and one had a side-to-side difference in knee laxity exceeding 3 mm and was therefore excluded, leaving 68 subjects in the control group. The mean age at examination, sex ratio, and general geographic living area of the controls were also similar to patients in the other cohorts (Table 2).

Some selection bias may have occurred among control subjects, in that the presence of knee symptoms among those invited could generate a greater interest in participating. However, the prevalence of radiographic knee OA in the control group was comparable with that observed in a general population in the same geographical area (Danielsson and Hernborg 1970).

Table 2. Demographics and surgical characteristics of the study cohorts

Characteristics	Year of meniscectomy 1973 N = 98	1978 N = 64	1983–1985 N = 155	Controls N = 68
Men, no. (%)	71 (72)	52 (81)	128 (83)	50 (74)
Age at index surgery, mean (SD) years	34 (11)	34 (10)	38 (12)	-
Age at follow-up, mean (SD) years	55 (11)	52 (10)	54 (12)	56 (12)
Follow-up time, mean (SD) years	21 (0.3)	18 (0.5)	16 (0.9)	-
Body mass index, mean (SD) kg/m^2	26 (4)	26 (3)	26 (3)	26 (4)
Medial meniscectomy, no. (%)	75 (77)	51 (80)	125 (81)	-
Degenerative meniscal tear, no. (%)	34 (35)	16 (25)	71 (46)	-
Arthroscopic technique, no. (%)	0 (0)	0 (0)	48 (31)	-
Total meniscectomy, no. (%)	96 (98)	47 (73)	11 (7)	-

Patient-relevant outcome—self-administered questionnaires should be used

For the patient and the care provider, the patient's knee function and symptoms should be considered more important, rather than the results of radiographic examination. Principally, in order to evaluate the patient's perspective of their knee, an investigator can ask questions, or the patient can complete a self-administered questionnaire.

The most common instruments used to evaluate long-term results of meniscal surgery are the Tapper and Hoover grading system (Tapper and Hoover 1969), the Lysholm Knee Scoring Scale (Lysholm and Gillquist 1982, Tegner and Lysholm 1985), and the International Knee Documentation Committee Knee Ligament Standard Evaluation Form (IKDC) (Hefti et al. 1993, Irrgang et al. 2001). However, the construction, score aggregation, mode of administration, and validity of these instruments have been questioned (Risberg and Ekeland 1994, Sgaglione et al. 1995, Bengtsson et al. 1996). Data regarding symptoms and function have been collected through interview, with a risk of bias being introduced by the observer (Lieberman et al. 1996, Höher et al. 1997, Roos 2001). The application of self-administered outcome measures is now promoted (Amadio 1993, Clancy and Eisenberg 1998), and a conceptual framework for outcomes research in arthroscopic meniscectomy has been published, emphasizing the use of patient-relevant outcomes such as the ability to walk, do housework, or be active in sports rather than measures of physical impairment (range of motion, effusion etc) (Small et al. 1994). Doctoral thesis work from Lund University resulted in a validated and responsive patient-relevant questionnaire, the Knee injury and Osteoarthritis Outcome Score (KOOS) (www.koos.nu; Roos 1999; Figure 5).

Figure 5. The front cover of the doctoral thesis from Lund University of patient-relevant outcome after knee injury and osteoarthritis.

Knee injury and Osteoarthritis Outcome Score

The KOOS was developed as an instrument to assess the patients' opinion about their knee and associated problems. The primary intention was to use it after knee injury that can result in OA.

The measure is a 42-item self-administered questionnaire, which fully contains and extends the Western Ontario MacMaster Universities Osteoarthritis Index (WOMAC) LK 3.0 (Bellamy et al. 1988). The WOMAC scores can thus be calculated. WOMAC is valid for elderly subjects with knee OA.

The KOOS comprises 5 subscales: Pain, other Symptoms, Activities of Daily Living (ADL), function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). A score from 0 to 100 is calculated for each dimension, with 100 representing the best result. The KOOS subscales Sport/Rec and QOL were more sensitive and discriminative than the WOMAC subscales Pain, Stiffness, and Function, when studied in subjects with radiographic knee OA, who had undergone meniscectomy 21 years ago, compared with controls matched for age and sex (Roos et al. 1999).

The measure has been proven valid for patients undergoing meniscectomy (Roos E M et al. 1998a), anterior cruciate ligament reconstruction (Roos E M et al. 1998b), and total knee replacement (Roos and Toksvig-Larsen 2003).

The patients were instructed to complete the KOOS form considering their operated knee (Paper I, II, and IV). Control subjects were asked to consider their knees in general.

In addition to the KOOS questionnaire, information on occupational workload and leisure physical activity level was collected for both patients and control subjects. The estimates were made retrospectively by the subject and divided into 5-year periods from the time of surgery until the time of assessment. Occupational load was graded as clerical work/unemployed/retired, light labor, moderate labor, or heavy labor. Leisure physical activity level was graded as low, moderate, high, or very high. Examples from each category were given in the questionnaire. Patients operated between 1983 and 1985 estimated only their current occupational workload and physical activity level.

Definition of a symptomatic knee

In order to define a symptomatic knee (Paper II and IV), I created a definition based on the patient's self-report from the KOOS questionnaire and consensus among the authors. This operational definition aimed at identifying individuals symptomatic enough to possibly seek medical care. The definition required that the score for the KOOS subscale QOL and 2 out of the 4 additional subscales should be equal to or less than the score obtained as follows: at least 50% of the questions within the subscale are answered with at least a one-step decrease from the best response (indicating no pain/ best possible function, etc.) on a 5-point Likert scale. After conversion to the 0–100 scale (0 = worst, 100 = best), the cutoffs were as follows: Pain ≤ 86.1, Symptoms ≤ 85.7, ADL ≤ 86.8, Sport/Rec ≤ 85.0, and QOL ≤ 87.5.

Short-Form 36-item Health Survey

To cover multiple aspects in the assessment of patients (Paper I), the use of both disease-specific and generic questionnaires is recommended (Small et al. 1994, Hawker et al. 1995, Altman et al. 1996).

The Medical Outcome Study 36-item Short-Form Health Survey (SF-36) is a widely used self-administered measure of general health assessing the following 8 dimensions: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health (Ware and Sherbourne 1992). A score from 0 to 100 is calculated, where 100 represents the best result.

The SF-36 has been used to evaluate subjects with anterior cruciate ligament injury (Shapiro et al. 1996) and after meniscectomy (Katz et al. 1992). I used the SF-36 Standard Swedish Version 1.0 (Sullivan and Karlsson 1994).

Radiographic evaluation—the most common method to define OA

Radiographic imaging is still considered the "golden standard" to define OA in epidemiological research. However, there is some controversy over the optimal imaging protocol (knee position, beam direction, etc.) and how to grade and interpret the radiographic findings (Boegard and Jonsson 1999). The most widely adopted OA grading system is originally described in 1957 by Kellgren and Lawrence. It incorporates osteophytes, joint space narrowing (JSN), and sclerosis in a 5-point OA scale (Kellgren and Lawrence 1957). The most common cutoff to define radiographic OA is Kellgren and Lawrence (K/L) grade ≥ 2.

In the present studies, I used the atlas of Osteoarthritis Research Society International (OARSI) for reading the films, scoring JSN and marginal osteophytes separately (Altman et al. 1995). These features can thus be studied independently. However, an OA definition incorporating both JSN and osteophytes has been proven to offer the most precise estimation of the association of risk factors with disease worsening and clinical OA (Felson et al. 1997a, LaValley et al. 2001). This was verified in the present work (Paper II).

Standardized radiographic procedures

Standing anteroposterior images of both knees in 15° of flexion and were obtained of patients and control subjects using a fluoroscopically positioned x-ray beam (Paper II–IV). Axial view of the patellofemoral joint was acquired with a vertical beam with the subject standing with the knee in 50° of flexion. Posterioanterior hand images were obtained from patients operated in 1973 or 1978.

A Siemens Basic Radiographic System (Siemens GmbH, Erlangen, Germany) with film-focus distance 1.4 m at 70 kV and 10 mA was used for patients operated in 1973 or 1978 (who were assessed in 1994 and 1995) and for the control subjects. For the patients who had undergone surgery between 1983 and 1985 (assessed in 2000), a Phasix 60 generator (CGR, Liège, Belgium) at 70 kV, 16 mA, and film-focus distance 1.5 m was used.

OA scoring

To ensure consistent assessment and avoid drift throughout the reading sessions, specific radiographs of both hands and knees within the study material were selected as reference material and read repeatedly.

The tibiofemoral compartments and the patellofemoral compartment of the knee were assessed for JSN and osteophytes according to the atlas of OARSI. The presence of these features was graded on a 4-point scale (range 0–3, with 0 = no evidence of bony changes or JSN). I did not score sclerosis, attrition, joint malalignment, or patellar subluxation. When the patient had undergone subsequent tibial osteotomy or arthoplasty for OA, JSN was regarded as grade 3 in the affected compartment. In these cases, the contralateral and patellofemoral compartment (if total arthroplasty) and osteophytes were assessed on preoperative images when available, otherwise recorded as missing data.

I read all knee radiographs within a period of 2 weeks, with films from patients and controls mixed and blinded to clinical details. The tibiofemoral images of the patients who had undergone surgery in 1973 or 1978 were also read previously by other observers (Roos H. et al. 1998, Roos et al. 2001). Interobserver reliability (kappa statistic) for these readings and present grading was $\kappa = 0.64$ for JSN and $\kappa = 0.61$ for the maximum grade of osteophyte in the compartment, with a complete agreement in 85% of the compartments for JSN and in 81% for osteophytes.

Similar to the knee radiographs, all hand images were assessed for JSN and osteophytes, but not sclerosis, erosions, or joint malalignment. One patient who had arthroplasty in the base of the thumb due to OA was regarded as JSN grade 3. In that case osteophytes were recorded as missing data.

Within a period of 3 weeks two trained observers separately assessed all distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, interphalangeal joint of the thumb (IP 1), and the first carpometacarpal (CMC 1) joint of both hands. The observers were blinded to surgical details, to each other's assessment, and to the patients' knee radiographs. Interobserver reliability was $\kappa = 0.88$ for JSN and $\kappa = 0.79$ for osteophytes with complete agreement in 95% of the cases for both features. All discrepancies were reread and data obtained from the consensus reading were used for analysis.

The cutoff for radiographic knee and hand OA

I considered radiographic OA to be present in a knee if any of the following criteria was achieved in any of the two tibiofemoral compartments, or in the patellofemoral compartment: JSN grade ≥ 2, or the sum of the two marginal osteophyte grades from the same compartment ≥ 2, or grade 1 JSN in combination with a grade 1 osteophyte in the same compartment. In the second study of this thesis I studied the presence of tibiofemoral OA only.

Patients who fulfilled the criterion for being symptomatic (as previously defined) *and* for having radiographic OA of the knee were classified as having *symptomatic* radiographic knee OA.

In the individual hand joints I considered radiographic OA to be present if any of the following criteria was fulfilled: JSN grade ≥ 2, or osteophyte grade ≥ 2, or JSN grade 1 in combination with an osteophyte grade 1. I classified a subject as having radiographic hand OA if at least one of the following criteria was fulfilled: the presence of radiographic OA (as defined above) in at least one DIP/PIP/IP 1 joint in each hand symmetrically (i.e., corresponding joints), or at least two DIP/PIP joints in the same hand in a pattern consistent with primary OA (in the same row or ray), or the CMC 1 joint bilaterally.

The knee and hand joint cutoffs approximate grade 2 OA, based on the K/L scale (Kellgren and Lawrence 1957).

Radiographic considerations—only long-lasting OA will be visible

The presence of JSN on conventional radiographs with a semiflexed knee may reflect the loss and (or) subluxation of meniscal tissue, not only loss of joint cartilage (Adams et al. 1999). However, meniscal extrusion is associated with OA of the knee, probably due to decreased tensile strength as a result of degenerative changes in the meniscal matrix and its supporting structures (Gale et al. 1999, Bennett and Buckland-Wright 2002).

In the present studies I regarded the presence of either JSN grade 1 or a single grade 1 osteophyte as too nonspecific to be classified as radiographic OA. However, recent findings suggest that K/L grade 1 may reflect emergent knee OA (Lachance et al. 2002, Hart and Spector 2003). I considered JSN grade 1 *and* a single grade 1 osteophyte within the *same* compartment as a sufficient criterion, consistent with K/L grade ~2. In addition, a sum osteophyte compartment score ≥ 2 in the absence of JSN was defined as radiographic OA, which is consistent with previous suggestions (Spector et al. 1993, Felson et al. 1997a). Thus, I have slightly adjusted the criteria for radiographic OA compared with previous studies from the department (Roos H et al. 1998, Roos et al. 2001).

In two of the reports within this thesis (Paper II and IV), I used the presence of radiographic knee OA, or the combination of radiographic knee OA and symptoms (as previously defined), to define morbidity. The latter group (with symptomatic radiographic knee OA) represents a clinically important subgroup, as these individuals are, at some stage, the most likely patients to be referred to an orthopedic specialist to be considered for surgical OA treatment. However, patients may very well suffer from disability due to early-stage knee OA, although definite radiographic features of the disease are absent. Therefore, the true study population with symptomatic OA is likely to be much larger than the prevalence figures reported in most epidemiological studies.

Statistical analysis

Basic statistics

Continuous data in unmatched groups were analyzed using Student's *t*-test (parametric) or Mann-Whitney *U*-test (non-parametric) as appropriate. Binary data in 2 x 2 tables were evaluated by Fisher's exact test. The Wilcoxon test or McNemar's test was used to compare matched data as appropriate (Paper I, II). The relative risks of patient-controls matched for age, sex, and body mass index (BMI) were estimated by the Mantel-Haenszel approach (Paper II). Interobserver reliability was evaluated using kappa statistic. I considered a p-value ≤ 0.05 as statically significant, and all tests were two-tailed.

Multivariate statistics

Univariate and multivariate effects, with respect to the main risk factors, of the KOOS subscales Sport/Rec and QOL (Paper I), were subjected to analysis of variance (ANOVA). Factors with a p-value of < 0.15 obtained from the univariate analysis were considered in the multivariate analysis.

The effects of the explanatory factors on the presence of radiographic knee OA, and the presence of symptomatic radiographic knee OA (Paper II), were analyzed by means of logistic regression. In the univariate analyses, the odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated. Further, those factors that showed a tendency of affecting the outcome (by indicating a p-value < 0.10 from the likelihood ratio test) were forwarded in a multivariate analysis. A final multivariate model included only significant factors.

The association between radiographic hand OA and radiographic knee OA (Paper III) was also analyzed by logistic regression, and the other explanatory variables (age [continuous], sex, BMI [continuous], occupational workload, spare-time physical activity level, meniscectomy compartment, and type of meniscal tear) were all entered in the model simultaneously.

To examine the relationship between each risk factor and the presence of radiographic knee OA, knee symptoms, or the presence of symptomatic radiographic knee OA (Paper IV), a crude OR was obtained using, as a reference group, the risk of disease among subjects who did not have each factor. To obtain a multivariate-adjusted OR with 95% CI for each risk factor, a logistic regression model was used, with the presence of disease as the dependent variable, and all other explanatory variables entered.

Summary of papers I–IV

Paper I: Patient-relevant outcomes 14 years after meniscectomy—influence of type of meniscal tear and size of resection

Objective – To study long-term patient-relevant outcomes after meniscectomy, a surgical procedure associated with a high risk of knee OA. Principal objectives were to compare traumatic with degenerative meniscal tear, and partial with subtotal meniscectomy, respectively.

Methods – I studied 205 patients who had undergone meniscectomy between 1983 and 1985. There was no previous knee surgery and all knees were stable. The type of meniscal tear and surgical resection was ascertained by review of medical records. Patients were followed up after 12–15 years by self-administered questionnaires, the generic SF-36 and the disease-specific KOOS.

Results – In a multivariate analysis, using Sports and Recreation Function and knee-related Quality of Life subscales of the KOOS questionnaire as dependent variables, patients with a degenerative tear scored significantly worse than individuals with a traumatic tear ($p \leq 0.001$). Also in unmatched subgroups and age- and sex-matched patients, subjects with degenerative lesions scored worse on the knee-specific outcome ($p \leq 0.02$) and SF-36 except for Social Functioning ($p \leq 0.04$). Subgroup analyses showed that patients who underwent subtotal meniscectomy for a degenerative tear scored significantly worse on the knee-specific outcome than individuals who had a partial meniscectomy for the same type of tear ($p \leq 0.02$).

Conclusion – The long-term outcome of meniscal injury and surgery appears to be determined largely by the type of meniscal tear. Furthermore, my findings support the use of minimal meniscal resections in the treatment of degenerative tears. I suggest that the disease processes associated with the development of OA of the joint cartilage may also be active in the meniscus, and that a tear in a meniscus with degenerative changes might be regarded as the first sign of OA of the joint.

Paper II: Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis—a 16-year follow-up of meniscectomy with matched controls

Objective – To investigate long-term radiographic and patient-relevant outcome of isolated limited meniscectomy with regard to type of meniscal tear and extent of surgical resection.

Methods – I studied 155 patients with intact cruciate ligaments, mean age (SD) 54 (12) years, who had undergone meniscectomy an average 16 (1) years earlier. The patients were examined using standardized radiography and validated self-administered questionnaires. The KOOS was used to quantify knee-related symptoms, and the definition of a symptomatic knee was determined. I used 68 control subjects matched for age, sex, and BMI to calculate the relative risks.

Results – Radiographic tibiofemoral OA (K/L grade ≥ 2) was present in 66 index knees (43%), of which 39 (59%) were considered to be symptomatic according to the KOOS. In total, 77 patients (50%) had a symptomatic index knee. In a multivariate model, degenerative meniscal tears were associated with both radiographic OA ($p = 0.03$) and symptomatic radiographic OA ($p = 0.02$). The relative risks for symptomatic radiographic OA after degenerative and traumatic types of meniscal tear were 7.0 (95% CI 2.1–23) and 2.7 (95% CI 0.9–7.7), respectively, compared with matched controls.

Conclusion – An isolated meniscal tear treated by a limited meniscectomy is associated with a high risk of radiographic and symptomatic tibiofemoral OA at 16-year follow-up. Factors associated with worse outcome were degenerative meniscal lesions and extensive resections. I suggest that degenerative meniscal tears may be associated with incipient OA, and that the meniscal tear signals the first symptom of the disease.

Paper III: Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy

Objective – To evaluate the association between radiographic hand OA, a disease with marked heredity, and radiographic knee OA in patients treated with meniscectomy.

Methods – I retrospectively identified 170 patients (mean age 54 [33–87] years, 23% women) who had undergone isolated meniscectomy an average 20 (17–22) years earlier. Patients with cruciate ligament injury were excluded. All subjects were examined by standardized knee and hand radiography. Individual joints were considered to have OA when displaying radiographic features corresponding to K/L-grade ≥ 2. Hand OA was considered present if at least one of the following criteria was fulfilled: the presence of radiographic OA (K/L grade ≥ 2) in at least 1 IP joint in each hand symmetrically, or in at least 2 DIP or PIP joints in the same hand in a pattern consistent with primary OA (in the same row or ray), or in the CMC I joint bilaterally. The association between radiographic hand OA and radiographic knee OA was evaluated using logistic regression.

Results – Radiographic hand OA was present in 57 patients (34%) and radiographic knee OA was identified in 105 patients (62%), in 94 index knees (55%) and 47 contralateral knees (28%). In a multivariate model, radiographic hand OA was associated with an increased likelihood of radiographic OA in the index knee (OR 3.0, 95% CI 1.2–7.5) and in the nonoperated contralateral knee (OR 3.5, 95% CI 1.0–12).

Conclusion – The presence of radiographic hand OA is associated with an increased frequency of radiographic knee OA after meniscectomy. This finding confirms and extends that of a single previous study showing an interaction between hereditary and environmental risk factors for OA, a common and genetically complex disease. Accordingly, the development of OA following a meniscal tear and the resulting meniscal surgery should not be regarded to be of secondary origin only.

Paper IV: Risk factors for symptomatic knee osteoarthritis 15–22 years after meniscal resection

Objective – To evaluate, after meniscal resection, the contributing influence on the development of radiographic knee OA and symptomatic radiographic OA of age, sex, BMI, extent of meniscal resection, localization and type of meniscal tear, cartilage status, and knee load at work and leisure.

Methods – I evaluated 317 patients with no cruciate ligament injury (mean [SD] age 54 [11] years) who had undergone isolated meniscal resection 15–22 years earlier (identified retrospectively, follow-up rate 70%) with radiographic and clinical examination. The validated and self-administered KOOS questionnaire was used to quantify knee-related symptoms. I used 68 nonoperated subjects identified from National Population Records as a reference group.

Results – Radiographic tibiofemoral OA (corresponding to K/L-grade ≥ 2) was present in 152 operated knees (48%) and 6 control knees (9%; relative risk 5.4, 95% CI 2.5–13). Using logistic regression, patients undergoing total meniscectomy (OR 3.4, 95% CI 1.4–9.3) and subjects with obesity (BMI ≥ 30, OR 2.5, 95% CI 1.1–5.7) had a greater likelihood of radiographic tibiofemoral OA than subjects operated on with partial meniscal resection and BMI < 25, respectively. Furthermore, degenerative meniscal tear (OR 2.9, 95% CI 1.6–5.4), peroperative cartilage changes (OR 2.6, 95% CI 1.2–5.9), and lateral meniscectomy (OR 2.4, 95% CI 1.2–4.7) were associated with radiographic OA more frequently than longitudinal tear, no peroperative cartilage changes, and medial meniscectomy, respectively. Symptomatic radiographic tibiofemoral or patellofemoral OA was associated with obesity (OR 3.9, 95% CI 1.6–9.9), female sex (OR 2.9, 95% CI 1.4–6.0), and degenerative meniscal tear (OR 2.5, 95% CI 1.2–5.1).

Conclusion – OA development after meniscal resection is regulated by the interplay between systemic factors and local biomechanical factors. A partial meniscal resection induces less radiographic change over time than does total meniscectomy, but not less symptoms. Obesity, female sex, and a degenerative type of meniscal tear are factors associated with poor self-reported and radiographic outcome. I suggest that the degenerative meniscal tear may be the first “signal” feature of early-stage knee OA.

Results and discussion

The risk of OA after meniscectomy is high

Large prospective studies have confirmed knee trauma to be a significant risk factor for knee OA (Gelber et al. 2000, Wilder et al. 2002). The reported relative risks are in the range of 5 to 7, probably depending on age at entry of the study population, different exposure definitions, and the different criteria for OA used in these studies. In the present work, I used the exposure definition of meniscal resection as documented by surgical records, not a self-report of knee trauma. In fact, knee trauma is far from always present in patients with a surgically treated meniscal lesion. In my material of subjects without associated cruciate ligament injury, about 50% had an insidious onset of symptoms (Paper I).

In the study cohorts, comprising patients who had undergone total, subtotal, or partial meniscectomy, I generally found a high prevalence of knee OA. Tibiofemoral radiographic OA corresponding to K/L grade ≥ 2 was present in 48% of the index knees and in 26% of the contralateral knees (Paper IV). In the controls, equally 6 right and 6 left knees (9%) were affected (Figure 6). The overall relative risk of developing radiographic tibiofemoral OA was 5.4 (95% CI 1.4–7.5) for the index knee compared with the group of controls, and the corresponding relative risk of developing symptomatic radiographic knee OA (tibiofemoral or patellofemoral) was 3.7 (95% CI 1.6–10).

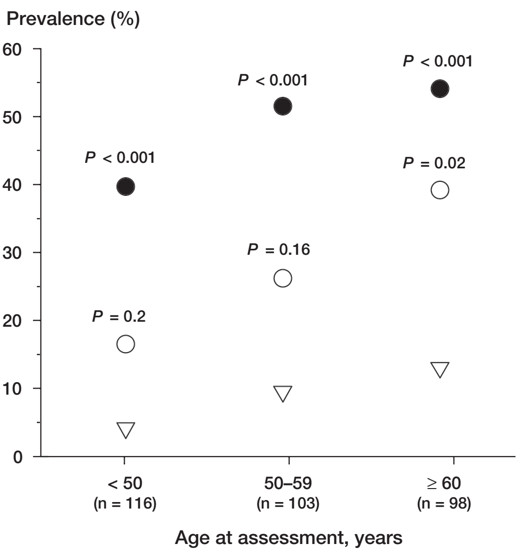

Figure 6. Prevalence of tibiofemoral radiographic osteoarthritis in meniscectomized patients (n = 317) 15–22 years after meniscal resection and in nonoperated control subjects (n = 68); the operated (index) knee (●), the contralateral knee (○), and the control knees (▽). P-values were determined by Fisher's exact test and indicate significance of the difference compared with control subjects.

A previous literature review revealed a considerable variation in knee OA prevalence reported after meniscectomy (Lohmander and Roos 1994). In the retrospective reports, about 20–70% of the patients have been found to have radiographic changes consistent with OA 5–30 years after their meniscectomy (Fairbank 1948, Johnson et al. 1974, Allen et al. 1984, Neyret et al. 1993, Rockborn and Gillquist 1996). The reasons for the variation could be several. Most studies show a considerable dropout rate, associated injuries are often not described or taken into account, and radiographic classification of OA is highly varying. These factors make comparisons of the disease prevalence difficult. Most studies from Northern Europe use the radiographic OA classification described by Ahlbäck, which is based on the presence of JSN and bone attrition (Ahlbäck 1968). This grading system does not take osteophytes into account, and thus valuable information may have been lost.

The long-term prospective studies after meniscectomy are sparse. One study of 86 athletes showed that 89% had developed radiographic changes (according to the Ahlbäck or Fairbank grading systems) 12–21 years after the meniscectomy (Jørgensen et al. 1987). Another prospective study of isolated meniscectomy (n = 180) found that 33% had narrowing of the joint space and 13% osteophyte formation after 6–10 years, using the Fairbank grading system (Hede et al. 1992a).

Table 3. Analysis of risk factors for patients who had undergone meniscal resection between 1983 and 1985. Univariate and multivariate effects of main factors on the Knee injury and Osteoarthritis Outcome Score (KOOS) dimension knee-related Quality of Life (QOL); results from ANOVA. The results were similar for function in Sport and Recreation

Explanatory factor	N	Univariate estimate [b] (95% CI)	P	Multivariate estimate [b] (95% CI)	P
Sex					
Woman [a]	45	0	0.1	0	0.08
Man	160	7 (-2, 15)		7 (-1, 16)	
Age at surgery (years)					
≤ 30 [a]	62	0	0.9	– [c]	
30-40	70	-2 (-10, 7)			
> 40	73	-2 (-11, 7)			
Compartment					
Medial [a]	167	0	0.4	– [c]	
Lateral	38	4 (-5, 13)			
Type of meniscal tear					
Traumatic [a]	85	0	< 0.001	0	< 0.001
Degenerative	89	-15 (-23, -8)		-15 (-23, -8)	
Other	31	-6 (-16, 4)		-5 (-15, 5)	
Technique of surgery					
Open [a]	143	0	0.5	– [c]	
Arthroscopy	62	-3 (-10, 5)			
Type of resection					
Partial [a]	83	0	0.6	– [c]	
Subtotal	122	-2 (-9, 6)			

95% CI = 95% confidence interval.
[a] Reference category.
[b] An estimate reflects the expected change of the dependent variable in relation to the reference category, e.g., men had an expected KOOS QOL that was 7 points (95% CI: -2 to 15 points) higher than for women, if no other factors were considered simultaneously (univariate analysis).
[c] Only factors with a p-value less than 0.15, obtained from the univariate analysis, were included in the multivariate analysis.

Type of meniscal tear largely determines the long-term outcome

In the first evaluation of the patients operated between 1983 and 1985 (Paper I), I found that subjects with a degenerative type of meniscal tear scored worse on the KOOS (Table 3, Figure 7) and the SF-36 (Figure 8) than did patients after a traumatic (longitudinal) tear. Also, when considering patients with radiographic knee OA only, a worse patient-relevant outcome was found after a degenerative type of meniscal tear (Figure 9) (Paper II). Furthermore, it is noteworthy that all 8 subjects who had undergone subsequent OA-related knee surgery (high tibial osteotomy or arthroplasty) in that cohort had a degenerative type of meniscal tear at index surgery.

The increase in risk of developing symptomatic radiographic knee OA was found to be 7-fold after a degenerative type of meniscal tear compared with nonoperated controls (Table 4). Multivariate analysis confirmed the degenerative meniscal lesion to be the strongest predictor of symptomatic radiographic knee OA in patients with a limited meniscal resection (OR 2.9, 95% CI 1.2–6.8 compared with longitudinal tears) (Paper II).

Already in the mid 1970s Noble reported that nearly half of the patients with a degenerative meniscal tear had persistent complaints, usually pain after meniscectomy (Noble 1975), and he concluded: “The horizontal cleavage lesion probably exists much more commonly than symptoms arising from it. Therefore, other factors must be involved in the production of symptoms.” Noble

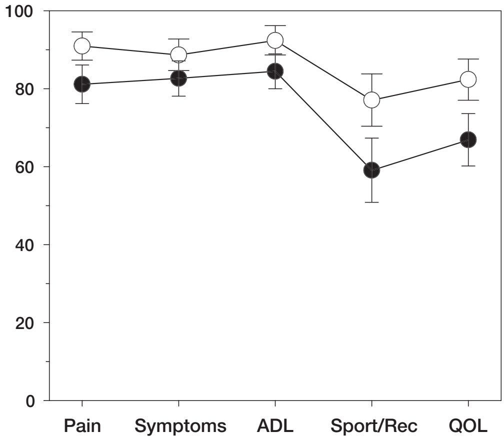

Figure 7. Knee injury and Osteoarthritis Outcome Score 14 years after meniscal resection according to traumatic (○) or degenerative (●) type of meniscal tear. The patients (operated between 1983 and 1985) are individually matched for age and sex (no. of pairs = 70). Bars show the 95% confidence interval. ADL = Activity of Daily Living, Sport/Rec = function in Sport and Recreation, QOL = knee-related Quality of Life.

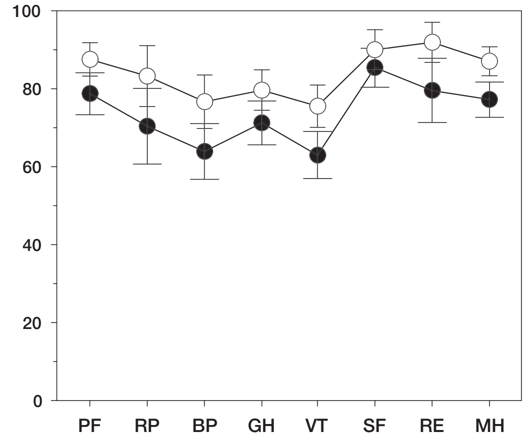

Figure 8. The results of the Short-Form 36-item Health Survey 14 years after meniscal resection according to traumatic (○) or degenerative (●) type of meniscal tear. The patients (operated between 1983 and 1985) are individually matched for age and sex (no. of pairs = 70). Bars show the 95% confidence interval. PF = Physical Functioning, RP = Role-Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role-Emotional, MH = Mental Health.

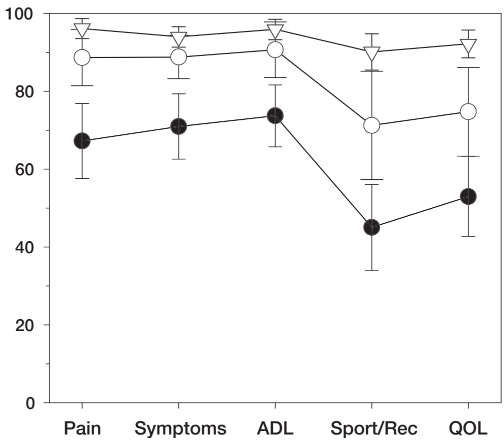

Figure 9. The mean Knee injury and Osteoarthritis Outcome Score in patients 16 years after surgery (operated between 1983 and 1985) with radiographic knee osteoarthritis (OA) stratified according to type of meniscal tear, traumatic (○, n = 21) or degenerative (●, n = 37). A reference group of nonoperated subjects (▽, n = 59) with no radiographic tibiofemoral OA is also shown. Bars show the 95% confidence interval. ADL = Activity of Daily Living, Sport/Rec = function in Sport and Recreation, QOL = knee-related Quality of Life.

and Hamblen also found an association between horizontal cleavages and osteoarthritic changes (Noble and Hamblen 1975). The worse outcome of the degenerative type of tear is consistent with previous observations from my department and from other groups (Faunø and Nielsen 1992, Neyret et al. 1994, Roos et al. 1995, Chatain et al. 2003).

The degenerative meniscal tear—a feature of early-stage OA

OA is a disease involving changes not only in joint cartilage, but the whole joint, including the meniscus (Pritzker 2003). Meniscal degenerative pathology has been correlated with degenerative cartilage changes (Bennett and Buckland-Wright 2002), and meniscal tears have been found to be highly prevalent in osteoarthritic knees, but having no clear effect on the patient's symptomatology and functional status (Noble 1975, Bhattacharyya et al. 2003). In present study, more reports of cartilage changes (early-stage OA) were noted at index surgery if a degenerative tear was present compared with a longitudinal meniscal tear (Paper IV).

Table 4. Relative risk of symptomatic tibiofemoral radiographic osteoarthritis 16 years after meniscal resection compared with nonoperated matched controls

	Type of meniscal tear			
	Degenerative (59 pairs)		Traumatic (57 pairs)	
Outcome for the operated knee	RR [a]	95% CI	RR [a]	95% CI
Symptomatic radiographic OA	7.0 [b]	2.1–23	2.7	0.9–7.7
Radiographic OA	5.3	2.4–12	3.2	1.4–7.3
Symptomatic	2.5 [b]	1.6–4.0	1.6	1.0–2.7
JSN grade ≥ 2	9.5	2.2–41	4.0	0.8–19
Sum osteophyte compartment score ≥ 2	10	2.3–43	7.0	1.8–28

[a] Relative risks (RRs) determined with McNemar's test and 95% confidence intervals (95% CIs) were obtained by comparing patients with controls matched for age, sex, and body mass index. For tibiofemoral joint space narrowing (JSN) and sum osteophyte compartment score, the most affected compartment was used for analysis.
[b] Patient-relevant outcome for one patient was missing.

On the basis of the results of present and previous studies, I suggest that a tear in a meniscus with degenerative changes is often associated with preexisting structural changes in the articular cartilage that may represent early-stage OA. The cartilage changes may or may not be visible at arthroscopy. Early proteolytic degradation of the collagenous meniscal matrix may result in decreased tensile strength. A meniscal tear could be the result of the therefore compromised meniscus' decreased ability to withstand loads and force transmissions during normal knee joint loads. A lesion may develop spontaneously or in conjunction with minor knee trauma (e.g., when rising from squatting position). Patients with meniscal symptoms due to a degenerative tear may thus constitute a subpopulation enriched in individuals with incipient OA. Depending on how much functionality of the meniscus that was lost due to the tear and the surgical procedure, the OA development may then progress further through increased biomechanical loading of the joint cartilage.

Meniscal protrusion is common in osteoarthritic knees (Adams et al. 1999, Gale et al. 1999). It is probably another, more advanced, sign of a degraded meniscus and the OA disease process, due to the loss of tensile strength of the meniscal matrix and its supporting structures reducing the hoop tension when the meniscus is loaded.

Knee OA after meniscal injury is not secondary OA only

Several studies have shown an association between OA of the hand and OA of the knee, suggesting that hand OA is often part of a more generalized OA (Cushnaghan and Dieppe 1991, Hart et al. 1994, Hirsch et al. 1996). Hand OA has a significant heredity, indicating the presence of a genetic risk factor (Stecher 1941, Spector et al. 1996, Jonsson et al. 2003) (Figure 10). The only previous study investigating an association between hand OA and knee OA in individuals who had undergone meniscectomy, as a human model of isolated joint damage, was published in the early 1980s (Doherty et al. 1983). This study was the first to suggest an interaction between local joint injury and systemic factors in OA. Thus, the classic view of secondary OA may be incorrect and the distinction from primary OA not as clear as previously thought.

However, the report has drawn relatively little attention, at least in the orthopedic community. Some limitations associated with the study provided a rationale for the present investigation: a heterogeneous study group with regard to injury type and extent, a wide range of time since surgery, a high dropout rate, and evaluation of radiographic severity being confounded by disease prevalence. Furthermore, the type of meniscal tear was not evaluated and the radiographic criteria used to consider a diseased joint are difficult to interpret.

Figure 10. Generalized osteoarthritis (OA). The 57-years old male patient is operated due to a degenerative type of meniscal tear 18 years earlier and has bilateral symptomatic radiographic knee OA. Posterioanterior hand radiographs reveal the presence of polyarticular symmetrical hand OA predominantly affecting his distal interphalangeal joints.

Table 5. The association between radiographic hand osteoarthritis (OA) and radiographic knee OA 20 years after meniscectomy

	Index (operated) knee (n = 170)			Contralateral nonoperated knee (n = 130)		
Radiographic hand OA [a]	Knee OA, no. (%)	OR	95% CI	Knee OA, no. (%)	OR	95% CI
Absent (reference category)	53/113 (47)	1.0		9/86 (10)	1.0	
Present; crude estimate	41/57 (72)	2.9	1.5–5.8	17/44 (39)	5.4	2.1–14
adjusted for age, sex, and BMI		2.9	1.3–6.4		2.6	0.9–7.5
adjusted for all variables [b]		3.0	1.2–7.5		3.5	1.0–12

OR = odds ratio, 95% CI = 95% confidence interval, BMI = body mass index.
[a] See Patients and Methods for the definition of radiographic hand OA.
[b] Age, sex, BMI, occupational workload, spare time physical activity level, meniscectomy compartment, and type of meniscal tear.

In the present study (Paper III), I confirm the association between radiographic hand OA and radiographic knee OA after meniscal injury, for both the operated and the nonoperated knee (Table 5). A degenerative type of meniscal tear was more frequently found at index surgery in patients with radiographic hand OA (Table 6). Furthermore, patients with bilateral radiographic knee OA had radiographic hand OA more frequently than did patients with unilateral disease (61% vs. 35% $p = 0.01$). These findings provide additional support for an interaction between genetic and environmental risk factors for OA. As a consequence, degenerative joint disease after meniscectomy should not be considered to be a single entity or secondary OA only. Many patients undergoing meniscal surgery seem to carry an inherited OA tendency, and the meniscal tear merely represents the first "signal" feature of the disorder.

Table 6. Comparison between subjects, with and without radiographic hand osteoarthritis (OA), who have undergone meniscectomy approximately 20 years earlier

	Radiographic hand OA [a]		
	Present (n = 57)	Absent (n = 113)	P
Demographic data			
Age at assessment, mean (SD) years	61 (9)	50 (9)	< 0.001
Sex, no. (%) men	45 (79)	86 (76)	0.8
Body mass index, mean (SD) kg/m^2	26 (3)	26 (4)	0.9
Time since surgery, mean (SD) years	20 (2)	20 (2)	0.4
Occupational workload, median	clerical	light labor	0.2
Spare time physical activity level, median	moderate	moderate	0.7
Medial meniscectomy, no. (%)	50 (88)	83 (73)	0.05
Meniscal tear, no. (%) degenerative	27 (47)	29 (26)	0.006
Total meniscectomy, no. (%)	50 (88)	99 (88)	1.0
Radiographic outcome			
Radiographic OA in either knee, no. (%)	46 (81)	59 (52)	< 0.001
Radiographic OA in index knee, no. (%)	41 (72)	53 (47)	0.002
OA score, mean (SD) [b]	4.0 (3.4)	2.6 (2.6)	0.004
JSN, mean (SD) [c]	1.1 (0.9)	0.7 (0.8)	0.004
Osteophytes, mean (SD) [d]	1.6 (1.2)	1.1 (1.2)	0.01
Radiographic OA in nonoperated knee, no. (%) [e]	17 (39)	9 (10)	< 0.001
OA score, mean (SD) [b]	2.0 (2.3)	0.7 (1.2)	< 0.001
JSN, mean (SD) [c]	0.6 (0.6)	0.2 (0.5)	< 0.001
Osteophytes, mean (SD) [d]	0.9 (0.8)	0.3 (0.6)	< 0.001

[a] See Patients and Methods for the definition of radiographic hand OA.
[b] The sum of *all* joint space narrowing (JSN) grades and osteophyte grades in the knee.
[c] The highest grade of JSN from the knee compartments.
[d] The highest sum of the marginal osteophyte grades from the knee compartments.
[e] Patients with meniscectomy in the contralateral knee (n = 39) are excluded.

High biomechanical load contributes to OA progression

Partial meniscectomy—less radiographic changes

Despite the impact of endogenous risk factors for the development and progression of knee OA in patients who have undergone meniscectomy, there are important biomechanical aspects that need to be addressed. To my knowledge, the fourth study of this thesis is the first, using large subject numbers, to show that partial meniscal resection induces less structural tibiofemoral changes related to OA than does total meniscectomy (Table 7). However, the frequency of symptomatic radiographic knee OA was not substantially lowered (Table 8), confirming that radiographic changes and clinical symptoms do not necessarily go hand in hand (Lethbridge-Cejku et al. 1995, Hannan et al. 2000).

As suggested by reports from Tapper and Hoover and some other investigators the preservation of an intact peripheral rim of the meniscus may produce better long-term results (Tapper and Hoover 1969, Northmore-Ball et al. 1983, Chatain et al. 2001, Andersson-Molina et al. 2002). If a substantial portion of the circumferentially oriented matrix fibers is intact, hoop tension may still develop, which counteracts meniscal extrusion when the knee is loaded. Substantial function of the residual meniscus in shock absorption and load transmission may thus remain. Any form of meniscal lesion or resection disrupting the circumferential continuity of the meniscus would compromise the major meniscal functions.

However, most reports of partial meniscectomy, including the only prospective study (Hede et al. 1992), have failed to demonstrate, or presented only very limited evidence, of a lower frequency

Table 7. Relationship of risk factors for the development of tibiofemoral radiographic osteoarthritis (OA) in the operated knee 15 to 22 years after meniscal resection (n = 317 of whom 152 cases with radiographic OA); results from logistic regression

Risk factors	Prevalence of tibiofemoral radiographic OA, no. (%)	Crude OR	Adjusted [b] OR	(95% CI)
Age at surgery (years)				
< 30 [a]	43/102 (42)	1.0	1.0	
30–39	48/97 (49)	1.3	1.6	(0.9–3.0)
≥ 40	61/118 (52)	1.5	1.2	(0.6–2.3)
Sex				
Men [a]	115/251 (46)	1.0	1.0	
Women	37/66 (56)	1.5	1.6	(0.8–3.0)
Body mass index (kg/m^2)				
< 25 [a]	55/126 (44)	1.0	1.0	
25-29	72/153 (47)	1.1	1.1	(0.6–1.9)
≥ 30	25/38 (66)	2.5	2.5	(1.1–5.7)
Follow-up time (years)				
15–18 [a]	96/217 (44)	1.0	1.0	
19–22	56/100 (56)	1.6	1.0	(0.5–2.1)
Technique of surgery				
Arthroscopy [a]	25/48 (52)	1.0	1.0	
Open surgery	127/269 (47)	0.8	0.5	(0.2–1.2)
Type of resection				
Partial [a]	27/64 (42)	1.0	1.0	
Subtotal	39/99 (39)	0.9	2.2	(0.9–5.0)
Total	86/154 (56)	1.7	3.4	(1.3–9.3)
Localization (compartment)				
Medial [a]	114/251 (45)	1.0	1.0	
Lateral	38/66 (58)	1.6	2.4	(1.2–4.7)
Tibiofemoral cartilage status				
Healthy [a]	119/272 (44)	1.0	1.0	
Changes	33/45 (73)	3.5	2.6	(1.2–5.9)
Type of meniscal tear				
Longitudinal [a]	49/138 (36)	1.0	1.0	
Degenerative	73/121 (60)	2.8	2.9	(1.6–5.4)
Radial	10/23 (43)	1.4	0.9	(0.3–2.4)
Healthy or non-classified	20/35 (57)	2.4	2.0	(0.9–4.6)

OR = odds ratio, 95% CI = 95% confidence interval.
[a] Reference category.
[b] Adjusted simultaneously for all other risk factors listed (for age, body mass index and follow-up time continuous data is used when adjusting the other factors).

of radiographic knee OA or functional improvements (Faunø and Nielsen 1992, Neyret et al. 1993, Burks et al. 1997, Higuchi et al. 2000, Andersson-Molina et al. 2002). In addition to the limitations associated with the reports after total meniscectomy, previous studies may have been affected by the use of short follow-up times, lack of adjustment for BMI, low patient numbers, and the patient-relevant outcome has been inadequately evaluated. Furthermore, the extent of meniscal resection is not an independent variable but is influenced by the extent and type of the meniscal tear.

Although there appears to be some benefit by preserving meniscal tissue, a dramatically reduced frequency of knee OA seems not to be the case, judging by today's evidence. The reason may be that many of the patients operated on already have incipient OA, as proposed in this thesis. The surgical intervention simply removes some of the evidence of the disorder, while the OA joint degradation proceeds.

Table 8. Relationship of risk factors for the development of symptomatic radiographic osteoarthritis (OA) in the operated knee 15 to 22 years after meniscal resection (n = 305 of whom 83 cases with symptomatic radiographic OA); results from logistic regression. The patellofemoral compartment is included in the definition of radiographic OA

Risk factors	Prevalence of symptomatic radiographic OA, no. (%)	Crude OR	Adjusted [b] OR	(95% CI)
Age at surgery (years)				
< 30 [a]	23/99 (23)	1.0	1.0	
30–39	24/93 (26)	1.1	1.3	(0.6–2.7)
≥ 40	36/113 (32)	1.5	1.3	(0.6–2.7)
Sex				
Men [a]	58/243 (24)	1.0	1.0	
Women	25/62 (40)	2.2	2.9	(1.4–6.0)
Body mass index (kg/m^2)				
< 25 [a]	23/122 (19)	1.0	1.0	
25–29	45/148 (30)	1.9	2.3	(1.2–4.6)
≥ 30	15/35 (43)	3.2	3.9	(1.6–9.9)
Follow-up time (years)				
15–18 [a]	53/215 (25)	1.0	1.0	
19–22	30/90 (33)	1.5	1.2	(0.6–2.6)
Technique of surgery				
Arthroscopy [a]	13/48 (27)	1.0	1.0	
Open surgery	70/257 (27)	1.0	1.1	(0.4–3.0)
Type of resection				
Partial [a]	17/64 (27)	1.0	1.0	
Subtotal	20/98 (20)	0.7	1.2	(0.5–3.2)
Total	46/143 (32)	1.3	1.6	(0.5–4.8)
Localization (compartment)				
Medial [a]	64/241 (27)	1.0	1.0	
Lateral	19/64 (30)	1.2	1.6	(0.8–3.3)
Tibiofemoral cartilage status				
Healthy [a]	62/261 (24)	1.0	1.0	
Changes	21/44 (48)	2.9	1.8	(0.8–3.9)
Type of meniscal tear				
Longitudinal [a]	21/132 (16)	1.0	1.0	
Degenerative	42/117 (36)	1.6	2.5	(1.2–5.1)
Radial	5/23 (22)	0.5	0.9	(0.3–2.9)
Healthy or nonclassified	15/33 (45)	1.9	3.3	(1.3–8.1)

OR = odds ratio, 95% CI = 95% confidence interval.
[a] Reference category.
[b] Adjusted simultaneously for all other risk factors listed (for age, body mass index and follow-up time continuous data is used when adjusting the other factors).

Lateral meniscectomy is worse than medial

The worse outcome after lateral meniscectomy (Table 7) (Paper IV) is in accordance with other reports (Johnson et al. 1974, Allen et al. 1984, Jørgensen et al. 1987, Hede et al. 1992b, McNicholas et al. 2000, Chatain et al. 2003). The lateral meniscus has been reported to carry higher load in the knee compared with the medial meniscus. Consequently, the loss of the lateral meniscus results in more cartilage contact stress, which may further facilitate the OA process (Figure 11) (Walker and Erkman 1975, Seedhom and Hargreaves 1979).

Obesity is a risk factor

I found an association between obesity and the presence of both radiographic knee OA and symptomatic radiographic knee OA (Table 7, 8) (Paper IV), consistent with previous reports (Spector et al. 1994, Manninen et al. 1996, Felson et al. 1997b, Gelber et al. 1999). I cannot rule out the possibil-

Figure 11. Bilateral lateral radiographic knee osteoarthritis. The 37-year old male patient has undergone subtotal meniscectomy of the lateral meniscus of his right knee 15 years earlier, followed by repeated meniscal resections also of the lateral meniscus in the left knee. The radiographs show osteophyte formation and joint space narrowing in the lateral compartment of both knees.

ity that some individuals in the material could first have developed OA and then became sedentary and obese. However, using retrospective estimates of weight, made by the subjects, I did not find such a cause and effect. Therefore, to encourage weight loss, is one of the most important recommendations to give obese patients at high risk of OA (Felson et al. 1992).

The link between obesity and OA is not entirely clear. The association between obesity and hand OA (Carman et al. 1994), and the high risk of knee OA predominantly among women with high BMI (Felson et al. 1997b), suggest that increased cartilage stress in obese subjects may not be the only explanation.

Heavy physical activity

In the Framingham Study high knee load at work and leisure has been reported to be a factor of significance in the development of incident radiographic or symptomatic knee OA (McAlindon et al. 1999). I did not find such an association in my material (Paper IV). However, methodological issues (difficulty for subjects to estimate knee load retrospectively) may have contributed to the result.

Asymptomatic radiographic OA is common

Previous reports have found a limited correlation between radiographic signs of OA and patient-relevant outcome (Lethbridge-Cejku et al. 1995, Creamer et al. 2000, Hannan et al. 2000), but little is known of how large the proportion is of patients with asymptomatic radiographic disease. I used the patient's self-report in the KOOS to establish a clinically relevant cutoff, in order to define symptomatic subjects. In the material nearly half of the patients defined as having radiographic knee OA were classified as asymptomatic (Figure 12). Even though advanced features of OA were noted on the knee radiographs of several of these subjects, the disease was silent and did not influence the knee function, as assessed by the KOOS. Furthermore, almost half of the patients who were symptomatic did not have radiographic knee OA.

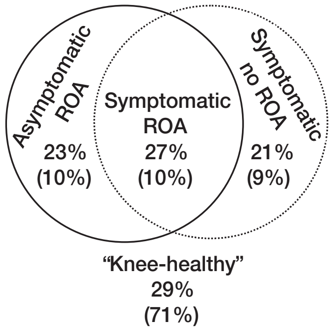

Figure 12. Prevalence and overlapping between radiographic osteoarthritis (ROA) and symptoms in the operated knee (n = 305) 15–22 years after meniscectomy. The percentages within brackets display the prevalence in control subjects (n = 68). The patellofemoral compartment is included in the definition of radiographic OA.

Several other causes than radiographic tibiofemoral or patellofemoral OA could explain knee complaints, but many patients are likely to suffer from symptoms of early-stage knee OA, even though definite features on conventional radiographs are absent (Lachance et al. 2002). Therefore, one of the challenges of future research will be to validate and standardize the criteria for "pre-radiographic" osteoarthritic disease (Figure 13).

Present study (Paper IV) corroborates Lagergren's finding that female sex was a risk factor for knee OA after meniscectomy (Lagergren 1943). In community based studies women are more prone to develop radiographic knee OA than are men (van Saase et al. 1989, Felson et al. 1997b). The strongest association in my material was obtained for symptomatic radiographic knee OA (Table 8). The cause of more symptoms in women is unclear but may involve muscular, neurophysiological, and psychosocial factors (McAlindon et al. 1993, O'Reilly et al. 1998, Creamer et al. 1999).

Meniscal surgery is often not indicated

With the introduction of arthroscopy, it may be that the indications for meniscal surgery have been liberalized. The low risk of complications and quick patient recovery have made the arthroscopic technique an attractive alternative to investigating and treating "meniscal" pain also in the older patient population. In my material, I have noticed an increase in the patient age at surgery with time, and consequently a gradual increase in the proportion of degenerative meniscal tears operated on. Furthermore, the increased use of diagnostic MRI, which very likely visualizes a meniscal tear, irrespective of whether the patient is symptomatic or not, contributes to a delicate situation for the arthroscopist (Bhattacharyya et al. 2003). It may be difficult not to operate even stable tears, if knee symptoms are

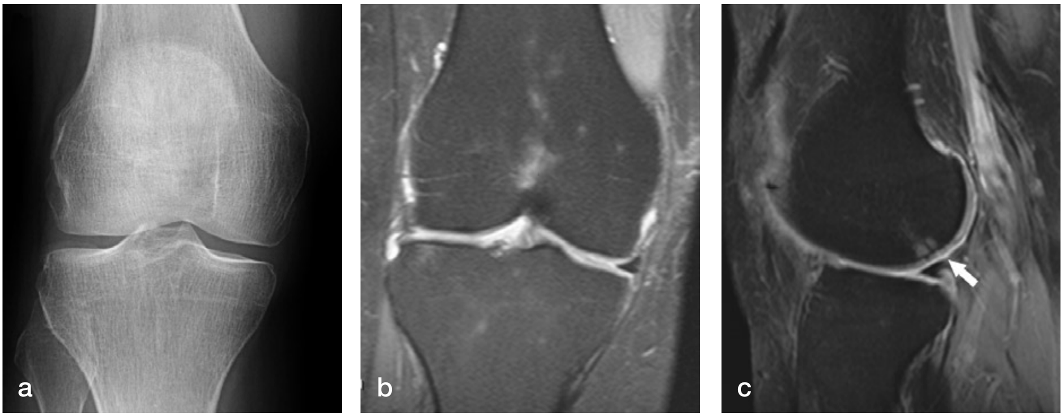

Figure 13. Example of the discrepancy between findings of conventional radiographic examination and magnetic resonance imaging (MRI). The patient, a 38-year old woman, has undergone subtotal lateral meniscectomy in her right knee 16 years earlier. The last year she has experienced aching related to joint use, relieved by rest. The frontal knee radiograph (a) shows normal findings, whereas coronal T2-weighted MRI (b) reveals status after subtotal lateral meniscectomy, and sagittal image (c) shows reduced cartilage thickness and bone marrow edema (arrow). Findings are compatible with early-stage knee OA.

present. Bearing in mind that the central 2/3 of the meniscus lack innervation, it may be difficult to discriminate between symptoms caused by a meniscal tear and symptoms of early-stage OA. The osteoarthritic disease process (and symptoms) may start at a much younger age than previously thought. The etiology of pain in OA is still unclear, but recent findings suggest that bone marrow lesions on MRI or soft tissue involvement are important factors (Felson et al. 2001, Hill et al. 2001).

If the degenerative meniscal lesion is regarded as representing incipient OA, it is not surprising that surgical intervention directed to the meniscus has little or no influence on long-term patient-relevant and radiographic outcome (Moseley et al. 2002, Bhattacharyya et al. 2003, Dervin et al. 2003). There is no evidence that leaving a degenerative tear causes OA or increases progression (Fahmy et al. 1983). In contrast, extensive removal of meniscal tissue, particularly coupled with degenerative changes, will lead to a disappointing result. In addition, the short-term benefit from meniscal surgery of these lesions may indeed be questioned, as several studies indicate poor results (Dandy and Jackson 1975, Noble 1975, Roos. et al. 2000). In joints without specific mechanical symptoms, meniscal surgery is often not indicated. Furthermore, the placebo effect of arthroscopy should not be underestimated (Moseley et al. 2003).

Conclusions

After radiographic and clinical evaluation of subjects, who have undergone isolated meniscal resection 15–22 years earlier, I conclude the following:

- About 50% have developed radiographic knee OA, but just over half of these patients have symptoms affecting their knee-related quality of life.
- Another 20% are symptomatic, but have not developed radiographic changes corresponding to definite knee OA.
- A degenerative meniscal lesion is associated with worse clinical and radiographic outcome compared with a traumatic tear and may indicate the presence of early-stage knee OA.
- The risk of *symptomatic* radiographic knee OA following meniscal resection increased 7-fold after a degenerative meniscal lesion compared with nonoperated control subjects.
- There is interaction between systemic factors and local biomechanical risk factors for the development of knee OA after meniscectomy.
- Having radiographic hand OA is associated with an increased likelihood of having radiographic knee OA. Therefore an inherited susceptibility to the disease contributes to the risk of knee OA after meniscal tear.
- Obesity is a contributing risk factor for both radiographic knee OA and *symptomatic* radiographic knee OA following meniscal resection.
- A partial meniscal resection induces less radiographic change associated with OA than does total meniscectomy, but the patient-relevant outcomes remain essentially the same.
- Lateral meniscectomy induces more radiographic changes associated with OA than does medial meniscectomy, but not necessarily more symptoms.
- Women develop more frequently *symptomatic* knee OA after meniscal resection than do men.

Future perspectives

Present and previous studies have shown that the short and long-term outcome of meniscectomy is not as good as generally assumed, even when using limited meniscal resections. I suggest that a degenerative meniscal lesion may be associated with early-stage knee OA, a slowly progressive disorder also involving the menisci. In some individuals, the tear may even represent the first "signal" feature of OA. It is then not surprising that treatment directed towards the meniscus only has limited influence on the outcome. The intervention simply removes evidence of the disorder, while the OA joint degradation proceeds. This patient category could benefit from information and guidance by arthritis instructors instead of meniscal surgery, and in the future possibly be offered treatment with disease modifying OA drugs.

The middle-aged and older patient population with "meniscal" pain and meniscal lesions represents a challenge for the health professional. It may be difficult to discriminate between discomfort caused by a meniscal tear and symptoms of early-stage knee OA. In osteoarthritic knees the relation between meniscal tears and knee pain is highly questionable. Therefore, in joints without specific mechanical symptoms, meniscal surgery is often not indicated. In order to establish clinical guidelines, appropriately designed randomized controlled studies using sham treatment are needed. The placebo effect of arthroscopic surgery should not be underestimated.

Summary

Meniscectomy is recognized as an important risk factor for the development of knee osteoarthritis (OA), a disease that traditionally has been considered as a simple ”wear and tear” phenomenon. However, despite numerous reports, little evidence has been presented that a limited meniscal resection, compared with a more extensive resection, reduces the risk of OA by preserving meniscal function. *Why?* This thesis provides one possible answer to that question.

I studied 3 cohorts of patients who in 1973, 1978, or between 1983 and 1985 had undergone isolated meniscectomy at Lund University Hospital, Sweden. Patients were reviewed clinically and by using standardized radiographic procedures 15–22 years after the surgical procedure. 68 subjects with no previous knee surgery, no clinical meniscal injury, and stable knees were used as controls. The subjects completed self-administered patient-relevant questionnaires, one generic, the Short-Form 36-item Health Survey, and one disease-specific, the Knee Injury and Osteoarthritis Outcome Score (KOOS). I used the patient’s self-report of the KOOS to establish a clinically relevant cutoff to define symptomatic patients.

In the first study of 205 patients, based on questionnaires, I found that the patient-relevant outcome was largely dependent on the type of meniscal tear, and not so much the extent of a limited meniscal resection. A degenerative type of meniscal tear was associated with more knee pain, worse knee-related quality of life, and lower sports and recreation function compared with a traumatic tear.

Using 155 patients in a 16-year follow-up, the degenerative meniscal lesion was found to be a major risk factor for developing radiographic knee OA. In this second report, the relative risk for the development of symptomatic radiographic knee OA after a degenerative meniscal lesion was found to be 7-fold compared with control subjects matched for age, sex, and body mass index.

In a third radiographic study comprising 170 patients, I evaluated the association of hand OA and knee OA, and found that knee OA after meniscectomy cannot be viewed as secondary OA only. If hand OA was present there was an increased likelihood of the patient having knee OA. The finding was independent of age and supports interaction between genetic and environmental risk factors for OA.

In the fourth and last study, I evaluated several candidate risk factors for the development of radiographic knee OA or symptomatic radiographic knee OA in a population of 317 individuals minimum 15 years after their meniscectomy. I found that partial meniscal resection induced less structural change related to knee OA compared with total meniscectomy. However, symptoms were not substantially affected by the extent of meniscal resection, confirming a limited correlation between radiographic features of the disease and the patient-relevant outcome. In the material about 50% of the patients had developed radiographic OA in their operated knee, but just over half of these were symptomatic. An additional 20% had symptoms, but did not have radiographic knee OA. Many of these patients were likely to suffer from early-stage knee OA, where typical structural changes (visible on conventional radiographic examination) had not yet developed. A meniscal tear of degenerative type and obesity were the factors most strongly associated with both radiographic knee OA and symptomatic radiographic knee OA.

I conclude that a degenerative meniscal tear is often associated with early-stage knee OA, a disorder also involving the meniscal tissue. The meniscal tear could be the result of the compromised meniscus’ decreased ability to withstand loads and force transmissions during normal knee joint loads. The lesion may thus represent the first ”signal” feature of this slowly progressive disorder. The challenge for the health professional is to discriminate between symptoms caused by a meniscal tear and those caused by OA. In joints without specific mechanical symptoms, meniscal surgery is often not indicated. The intervention merely removes evidence of the disorder, while the OA joint degradation proceeds.

Sammanfattning på svenska

Artros (ledsvikt) är en mycket vanligt förekommande ledsjukdom, som omfattar nedbrytning av ledbrosk och förändring i ledstrukturen i övrigt. Sjukdomen kan medföra symptom som smärta, svullnad och stelhet, vilket leder till nedsatt ledfunktion. I Sverige utförs det per år ca 15000 protesoperationer (utbyte till konstgjord led) p.g.a. artros.

Tidigare studier har visat att meniskopererade patienter har en hög risk att utveckla artros i det opererade knät. Syftet med denna avhandling var att studera långtidsprognos efter meniskskada och efterföljande meniskoperation, samt att försöka finna de riskfaktorer som är starkast förknippade med utveckling av sjukdomen artros.

Patienter, som blivit meniskopererade (utan samtidig korsbandsskada) vid Lunds Universitetssjukhus under åren 1973, 1978 eller 1983 till 1985, blev uppföljda mellan 15 till 22 år efter operationen. Undersökning gjordes med knäleds- och handröntgen, samt patienterna fick fylla i två olika frågeformulär som handlade om knäledssymptom, funktion och livskvalitet. Jag använde 68 individer som kontrollgrupp. Dessa hade inte någon menisk- eller korsbandsskada, och de hade inte blivit opererade i knäna.

I den första delstudien (enkätbaserad) fann jag att patienter opererade p.g.a. en *degenerativ* meniskskada (beroende på försvagning av meniskstrukturen) hade sämre långtidsresultat avseende smärta och livskvalitet relaterat till knät jämfört med patienter med en *traumatisk* meniskskada (efter vridvåld mot knät). Hur mycket meniskvävnad som kirurgen tog bort betydde inte så mycket för symptom och funktion på lång sikt.

Vid röntgenundersökning (delstudie två) visade det sig att individer med en degenerativ meniskskada också hade mer röntgenverifierad artros i knät jämfört med patienter med en traumatisk meniskskada. Risken för att utveckla symptomgivande röntgenologisk artros i det opererade knät var 7 gånger högre hos patienter med en degenerativ typ av meniskskada jämfört med personerna i kontrollgruppen.

I en tredje delstudie undersökte jag sambandet mellan förekomst av artros i fingrar och artros i knäleden. Artros i fingerlederna har visat sig vara ärftligt betingat, alltså i hög grad kan förklaras av genetiska faktorer. I materialet fann jag att patienter med s.k. handartros hade högre förekomst av artros i knäna. Resultatet var oberoende av ålder. Detta tyder på att förekomsten av artros i dessa två ledgrupper inte är oberoende av varandra. Det finns alltså en samverkan mellan genetiska faktorer och miljöpåverkan vid utvecklingen av knäledsartros efter meniskoperation.

I den fjärde och avslutande delstudien till denna avhandling undersökte jag förekomsten av artros hos 317 patienter, som fick hela eller delar av en av sina menisker bortopererad i genomsnitt 18 år tidigare. Jag fann att borttagandet av hela menisken, jämfört med en mer begränsad meniskresektion, var förenat med högre risk för strukturella förändringar (synliga på röntgen), men att dessa inte nödvändigtvis medförde ökade besvär från knät. De riskfaktorer som var starkast förknippade med symptomgivande röntgenverifierad artros var övervikt, att vara kvinna samt en degenerativ typ av meniskskada.

Av det totala antalet patienter hade ca 50% röntgenologisk artros i sitt opererade knä, men bara drygt hälften av dessa hade besvär. Ytterligare ca 20% hade symptom från sitt opererade knä, men saknade typiska röntgenförändringar. Många av dessa patienter kan ändå lida av artros. Det tar nämligen lång tid för strukturella förändringar, synliga på vanlig röntgen, att utvecklas. Resultatet visar alltså på ett relativt dåligt samband mellan vad röntgen visar och vad patienterna själva upplever.

Baserat på resultaten i detta avhandlingsarbete drar jag den huvudsakliga slutsatsen att den degenerativa meniskskadan kan vara första tecknet på knäledsartros, en sjukdom som involverar hela knäleden, inte bara ledbrosk. En menisk som är försvagad av degenerativa förändringar har också lättare för att gå sönder, t.ex. då en person reser sig från sittande på huk (då belastningen på menisken ökar).

Artros är en ledsjukdom som utvecklas långsamt och kan starta tidigt i livet, men det dröjer innan sjukdomen syns på vanlig röntgen. Meniskskador är vanliga hos individer i övre medelåldern och hos äldre personer, men betyder inte så mycket för symptom och funktion. Svårigheten för sjukvården kan därför vara att skilja på vad som är en symptomgivande meniskskada, och vad som är tidiga symptom från sjukdomen artros. Degenerativa meniskskador, som inte orsakar besvär som låsningar eller upphakningar i knäleden, bör troligen inte behandlas kirurgiskt.

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