LONG-TERM CONSEQUENCES OF DEGENERATIVE MENISCAL TEARS IN MIDDLE-AGED PATIENTS

PhD Thesis

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Abbreviations

ACL	Anterior cruciate ligament
ADL	Activities of daily living
ANCOVA	Analysis of covariance
APM	Arthroscopic partial meniscectomy
BMI	Body mass index
BIC	Bayesian information criterion
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COSMIN	Consensus-based Standards for the Selection of health Measurement Instruments
ICF	International Classification of Function
IKDC	The International Knee Documentation Committee Subjective Knee Form
J	Joule
JSN	Joint space narrowing
JSW	Joint space width
fJSW	Fixed joint space width
K&L	Kellgren and Lawrence
kg	Kilograms
KOOS	Knee injury and Osteoarthritis Outcome Score
MIC	Minimal important change
MRI	Magnetic resonance imaging
N·m	Newton meter
OA	Osteoarthritis
OARSI	The Osteoarthritis Research Society International
OR	Odds ratio
OMERACT	The Outcome Measures in Rheumatology
OMEX	Odense Oslo Meniscectomy versus Exercise trial
SF-36	36-Item Short Form Health Survey
Sport/rec	Sport and recreational function
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
QoL	Quality of life

Abstract

Background

Degenerative meniscal tears represent an early sign of knee osteoarthritis (OA). Arthroscopic partial meniscectomy (APM) has been the usual treatment for symptomatic tears, but studies have found no additional benefit compared to exercise therapy. APM is a risk factor for knee OA development, but it remains unknown whether the increased risk is due to the meniscal tear per se or resection of the meniscus.

Aims

The overall aim of this thesis was to evaluate and compare long-term (five-year) consequences of APM and exercise therapy as treatments for degenerative meniscal tears. Specific aims were to (i) compare progression of radiographic OA changes and development of OA, (ii) compare changes in patient-reported outcomes, (iii) identify distinctive pain and knee function trajectories, and explore prognostic factors for sport and recreational function, and (iv) compare longitudinal knee muscle strength changes and explore associations between baseline knee muscle weakness and OA progression.

Methods

In the randomized controlled Odense Oslo Meniscectomy versus Exercise (OMEX) trial, 140 participants aged 35-60 years with degenerative meniscal tears and no or minimal radiographic OA were randomized to APM or exercise therapy. Standardized radiographs were acquired at baseline and five-year follow-up. Radiographic outcomes included semi-quantitatively assessed joint space narrowing and osteophytes, quantitatively assessed medial fixed joint space width, and OA incidence (defined as Kellgren and Lawrence grade <2 at baseline and grade ≥2 at follow-up). Patient-reported pain and knee function were assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS) at baseline, three, 12, and 24 months, and five years. In a secondary exploratory analysis study including all 140 OMEX trial participants, individual variation in pain and function changes were explored to identify subgroups following distinctive trajectories. Further, prognostic factors were examined for sport and recreational function trajectories. An isokinetic dynamometer was used to quantify quadriceps and hamstrings muscle strength at baseline, three and 12 months, and five years.

Results and conclusions

No strong evidence was found to support between-group differences in progression of

radiographic changes or knee OA development over five years. The incidence of radiographic OA was 16% in both treatment groups. Clinically relevant improvements in patient-reported pain and knee function were seen from baseline to five years following both treatments, but neither treatment was superior. Nine in every 10 participants improved pain and knee function early or gradually over two years. A small subgroup (10%-12% of the participants) with severe pain and functional limitations experienced no or minimal improvement over five years. For sport and recreational function, modifiable prognostic factors were identified. Body mass index, psychological factors, knee muscle strength, and functional performance might be appropriate therapeutic targets for early interventions. Exercise therapy was effective in improving knee muscle strength up to 12 months follow-up compared to APM, but between-group differences were attenuated at five years. Quadriceps muscle weakness at baseline was a risk factor for knee OA progression over five years.

Clinical implications

Degenerative meniscal tears can be regarded as an early sign of knee OA, but it develops slowly over time and the rate of radiographic OA is low five years after diagnosis. The findings in this thesis, both for radiographic and clinical outcomes, corroborate current clinical guidelines' stand against performing APM in this patient population. Individuals with degenerative meniscal tears need to be informed that similar results can be achieved following a 12-week exercise therapy program or APM, with additional benefits for knee muscle strength improvements following exercise. Finally, patient-education programs should also include that the majority of patients will experience early and clinically relevant improvements in pain and knee function.

Sammendrag

Bakgrunn

Degenerative meniskrupturer er et tidlig tegn på kneartrose. Artroskopisk partiell meniskreseksjon (APM) har vært den vanlige behandlingen for symptomatiske rupturer, men studier har ikke funnet noen ytterligere fordeler sammenlignet med treningsterapi. APM er en risikofaktor for utvikling av kneartrose, men det er uklart om den økte risikoen skyldes meniskrupturen i seg selv eller reseksjon av menisken.

Formål

Den overordnede hensikten med denne avhandlingen var å evaluere og sammenligne langtidskonsekvenser (fem-år) av APM og treningsterapi som behandlinger for degenerative meniskrupturer. De spesifikke målene var å (i) sammenligne progresjon av røntgenologiske artrose forandringer og utvikling av kneartrose, (ii) sammenligne endringer i pasientrapporterte utfallsmål, (iii) identifisere ulike forløp for smerte og knefunksjon, samt utforske prognostiske faktorer for funksjon i idrett og fritidsaktiviteter, og (iv) sammenligne longitudinelle endringer i muskelstyrke og undersøke sammenhenger mellom muskelstyrke ved inklusjon i studien og artroseprogresjon over fem år.

Metode

I den randomiserte kontrollerte Odense Oslo Meniscectomy versus Exercise (OMEX) studien ble 140 deltakere i alderen 35-60 år med degenerative meniskrupturer og minimalt med røntgenologisk artrose randomisert til APM eller treningsterapi. Standardiserte røntgenbilder ble tatt ved inklusjon og ved oppfølgning etter fem år. Røntgenologiske utfallsmål inkluderte leddspaltereduksjon og osteofytter vurdert semi-kvantitativt, medial fixed joint space width vurdert kvantitativt, og insidens av artrose (definert som Kellgren og Lawrence grad <2 ved inklusjon og grad ≥ 2 ved oppfølgning). Pasientrapportert smerte og knefunksjon ble vurdert med Knee injury and Osteoarthritis Outcome Score (KOOS) ved inklusjon, tre, 12 og 24 måneder, og fem år. I en eksplorativ studie som inkluderte alle 140 deltakerne i OMEX studien ble individuell variasjon i smerte og funksjonsendringer undersøkt for å identifisere subgrupper som fulgte ulike forløp for endring over tid. Videre ble prognostiske faktorer undersøkt for ulike forløp for funksjon i sport og fritidsaktiviteter. Quadriceps og hamstrings muskelstyrke ble kvantifisert med isokinetisk dynamometer ved inklusjon, tre og 12 måneder, og fem år.

Resultater og konklusjoner

Det ble ikke funnet evidens som indikerer forskjell mellom behandlingsgruppene i progresjon av røntgenologiske artroseforandringer eller utvikling av kneartrose over fem år. Insidensen av røntgenologisk artrose var 16% i begge behandlingsgruppene. Begge behandlingene resulterte i kliniske relevante endringer i pasientrapportert smerte og knefunksjon fra inklusjon til fem år, men det var ingen forskjell mellom gruppene. Ni av ti deltakere erfarte redusert smerte og bedre knefunksjon tidlig eller gradvis over de to første årene. En liten gruppe (10%-12% av deltakerne) med betydelig smerte og funksjonsnedsettelser erfarte ingen eller minimal forbedring over fem år. Modifiserbare prognostiske faktorer ble identifisert for funksjon i sport og fritidsaktiviteter. Kroppsmasseindeks, psykologiske faktorer, muskelstyrke, og objektiv knefunksjon kan være potensielle behandlingsmål for tidlig intervensjon. Treningsterapi resulterte i forbedret muskelstyrke sammenlignet med APM opp til 12 måneder, men det var små forskjeller etter fem år. Lavere muskelstyrke i quadriceps ved inklusjon i studien var en risikofaktorer for artroseprogresjon over fem år.

Kliniske implikasjoner

Degenerative meniskrupturer kan anses som et tidlig tegn på kneartrose, men utvikles sakte over tid og andelen med røntgenologisk artrose fem år etter diagnosen er lav. Funnene i denne avhandlingen, både for røntgenologiske og kliniske utfall, underbygger kliniske retningslinjer som fraråder APM som behandling for denne pasientgruppen. Personer med degenerative meniskrupturer bør informeres om at tilsvarende resultater kan oppnås med et 12-ukers treningsprogram eller APM, og at treningsterapi resulterer i ytterligere fordeler for økt muskelstyrke. Utdanningsprogram for pasienter med degenerativ menisruptur bør også inkludere informasjon om at majoriteten vil erfare tidlige og klinisk relevante forbedringer i smerte og knefunksjon.

List of papers

I. Berg B, Roos EM, Englund M, Kise NJ, Tiulpin A, Saarakkala S, Engebretsen L, Eftang CN, Holm I, Risberg MA. Development of osteoarthritis in patients with degenerative meniscal tears treated with exercise therapy or surgery: a randomized controlled trial. *Osteoarthritis Cartilage*. 2020;28(7):897-906.

II. Berg B, Roos EM, Kise NJ, Engebretsen L, Holm I, Risberg MA. On a Trajectory for Success—9 in Every 10 People With a Degenerative Meniscus Tear Have Improved Knee Function Within 2 Years After Treatment: A Secondary Exploratory Analysis of a Randomized Controlled Trial. *J Orthop Sports Phys Ther*. 2021;51(6):289-297.

III. Berg B, Roos EM, Kise NJ, Engebretsen L, Holm I, Risberg MA. Muscle strength and osteoarthritis progression after surgery or exercise for degenerative meniscal tears: Secondary analyses of a randomized trial. *In revision, Arthritis Care Res (Hoboken)*

Introduction

Degenerative meniscal tears exist in approximately every third knee of middle-aged and older individuals in the general population.[1] While some experience severe knee pain and functional limitations,[2,3] meniscal changes are also widespread in asymptomatic individuals.[1,4] The presence of a degenerative meniscal tear is an early sign of knee osteoarthritis (OA) and constitutes a strong risk factor for progression to more severe OA changes and disease development.[5-8]

Knee arthroscopy for degenerative knee diseases is one of the most frequently performed orthopedic surgeries.[9] Approximately two million procedures were performed in England from 1997 to 2017.[10] Arthroscopic partial meniscectomy (APM) comprised more than half of these operations. In several other countries, high and increasing rates of APM were reported in the first decade of the 21st century.[11-14] In Norway, the rate was 256 per 100 000 in 2012.[15] However, the effectiveness of the procedure has been challenged in several trials, and surgery rates have declined in recent years.[15-17] A 36% reduction was observed in Norway from 2012 to 2016.[15] Yet despite the scientific scrutiny the procedure has attracted, APM is still widely performed in the treatment of degenerative meniscal tears.[10,18]

Several high-quality randomized controlled trials have compared APM with exercise therapy or sham surgery in patients with or without established knee OA.[19-33] Exercise therapy is well tolerated with few adverse events reported[23,26] and may be cost-effective compared with APM.[34] Twelve weeks of twice-weekly exercise also provide additional benefits on muscle strength and functional performance.[26] No clinically relevant between-treatment differences have been found at follow-ups after one to five years in patient-reported outcomes.[19-24,26-33] The only exception is a time-limited benefit of APM on pain observed in one study.[25] On this basis, numerous systematic reviews[35-42] conclude that: (i) APM offers no additional benefit in patient-reported pain or knee function in comparison with exercise therapy or sham surgery, and (ii) surgery should not be the first-line treatment for middle-aged patients with degenerative meniscal tears with or without concomitant knee OA.

APM is a risk factor for radiographic knee OA.[43] Altered knee-joint biomechanics following meniscal resection may contribute to the elevated risk,[44] as abnormal load is the most common cause of OA.[45] However, increased knee OA risk is also found in degenerative meniscus individuals without previous surgery.[5] It is therefore not known whether the

increased risk is due to loss of meniscal function from the tear per se or resection of the meniscus. There is a rationale for reduced OA risk following exercise therapy without resection of the meniscus. First, the residual meniscus continues to distribute load across the knee joint.[46] Second, higher knee muscle strength may protect against knee OA development or progression to more severe OA changes.[47-49] The influence of treatment choice on long-term consequences is of particular importance for middle-aged individuals without established knee OA, as it would constitute a tremendous individual and socioeconomic burden.[50] OA was the 15th highest cause of years lived with disability worldwide in 2019, and the knee constitutes more than 60% of the global disease burden for OA.[51]

Irrespective of treatment, some degenerative meniscal tear patients do not respond to treatment and continue to experience severe pain and functional limitations long-term. Although substantial improvements in patient-reported pain and function have been demonstrated using the change score averaged over all patients,[19-33] this may overlook heterogeneity in treatment response among individual patients.[52] The presence of variability in outcomes is an indicator of treatment heterogeneity. When present, the observed average effect reflects a mixture of patients with substantial benefit, little benefit, and no benefit or deterioration.[53] Identifying subgroups with differential treatment responses could have considerable clinical implications. There may be potential prognostic factors associated with patients not responding to treatment. Ultimately, this would offer the opportunity to better individualize treatment to improve long-term outcomes. While some prognostic factors have been identified in surgically treated patients,[54] indicating that subgroups of patients with poor outcome exist, more research is needed on factors influencing treatment outcome.

The meniscus

Gross anatomy

The menisci are C-shaped fibrocartilaginous structures located on the medial and lateral aspects of the knee.[55,56] They are roughly triangular in cross-section, with the thicker outer rim attached to the joint capsule while the inner edge is thin and free.[56,57] The medial meniscus covers one-half and the lateral meniscus two-thirds of the corresponding tibial plateau (Figure 1).[56]

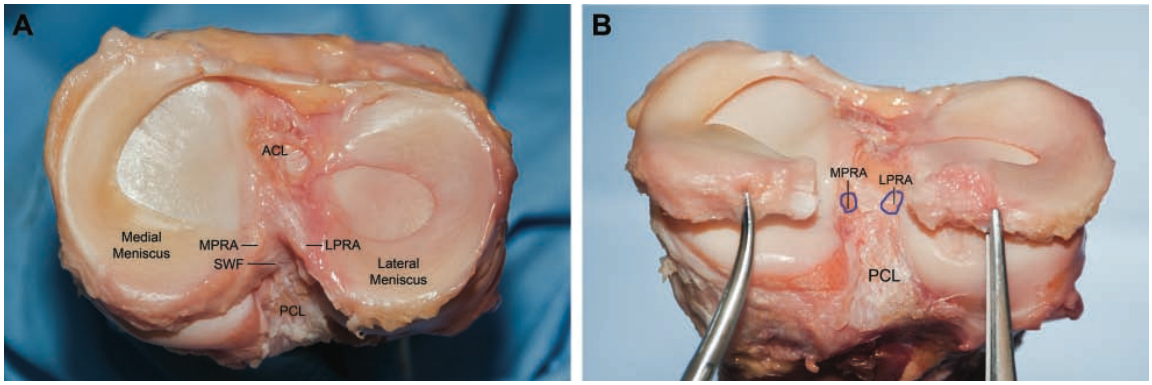

Figure 1. *Anatomical photographs demonstrating the relative size and attachments of the medial and lateral meniscus. (A) Superior view and (B) posterior view. ACL, anterior cruciate ligament; LPRA, lateral meniscus posterior root attachment; MPRA, medial meniscus posterior horn attachment; PCL, posterior cruciate ligament; SWF, shiny white fibers of posterior horn of medial meniscus. (From Johannsen et al.[58] with permission from SAGE Publication)*

The anterior and posterior meniscal horns anchor the menisci to tibial bone via insertional ligaments.[59] The medial meniscus anterior horn is attached at the intercondylar fossa anterior to the anterior cruciate ligament (ACL).[56] The posterior horn attaches just anterior to the tibial enthesis of the posterior cruciate ligament.[59] Additional firm attachment to the deep surface of the medial collateral ligament and the peripheral joint capsule makes the medial meniscus relatively immobile.[55] The lateral meniscus is more mobile as it does not have any direct attachment to the lateral collateral ligament, and the peripheral attachment to the joint capsule is interrupted by the popliteus tendon.[55] The anterior horn of the lateral meniscus attaches to the tibia just posterior to the ACL at the anterior intercondylar fossa.[59] The attachment of the posterior horn lies between the posterior cruciate ligament and the medial meniscus posterior horn.[56]

The menisci are relatively avascular. By maturity, only the peripheral 10% to 25% of the meniscal tissue is perfused.[60] The vascular region is called the red zone, whereas the completely avascular inner region of the menisci is called the white zone. The white zone is predisposed to degenerative tears since vascularization has important implications for the capacity to heal.[55] Most of the vascular supply to the menisci originates from the medial and lateral inferior and superior geniculate arteries.[61] The outer one-third of the meniscus body is also penetrated with neural elements, with heavier concentrations at the horns.[62,63] The innervation is received from the recurrent peroneal branch of the common peroneal nerve.[56]

Biochemistry and structure

The normal meniscus is composed primarily of water (70%-75%) and collagen (20%-22%).[64] Glycosaminoglycans and DNA are also present.[64] During the degenerative process, the content of water increases, whereas collagen and glycosaminoglycans decreases.[64,65] The meniscus primarily contains type I collagen, in contrast to articular cartilage, which mainly contains type II collagen.[66] The collagen fibers are predominately circumferentially oriented in the red zone, woven together with some radial oriented fibers in the superficial region to provide structural integrity. In the white zone, where both type I and II collagen are present, the collagens are cross-linked, which is ideal for transferring vertical compressive forces.[56]

Function

The function of the menisci is inextricably linked to their composition, structure, and morphology.[56] Load transmission and shock absorption during dynamic movements are the main functions.[57] The load-bearing function of the menisci first became evident through the observation of degenerative changes in knees following total meniscectomy.[67] Biomechanical studies later demonstrated that the menisci are responsible for more than 50% of load transmission across the joint.[68,69] The menisci responds to load with compression, and the circumferentially orientated collagen fibers transform axial load into hoop stresses at the meniscal periphery.[59] Shock absorption is provided by the viscoelastic properties of the tissue, where frictional drag forces occur as water escape the tissue.[56]

The crescent wedge shape of the menisci increases congruity between the femoral and tibial condyles, thereby providing stability in addition to increasing the contact area in the tibiofemoral joint.[56] The medial meniscus further contributes to anterior stability through the firm attachments to the medial collateral ligament and the joint capsule.[55,56] Due to the presence of mechanoreceptors, the menisci are not just passive stabilizers but also provides essential proprioceptive information enhancing motor control, dynamic stability, and coordination.[70]

Meniscal tears

Meniscal tears can be classified as traumatic or degenerative based on injury etiology or morphology.[71] Traumatic tears occur from excessive force to a normal meniscus, typically in the young active population.[71] Sports participation is, therefore, the strongest risk factor for

traumatic tears. They often occur concomitant with an ACL injury, and the rate of meniscal tears secondary to the index ACL injury is also high.[72] The combination of axial loading and rotational forces typically results in a longitudinal tear pattern, where the healthy meniscus splits vertically in line with the circumferentially oriented collagen fibers (Figure 2).[73] Radial tears are also most commonly traumatic in origin.[74]

In contrast to traumatic tears, normal forces acting on a degenerative structure may cause a degenerative tear.[71] Risk factors for degenerative meniscal tears include higher age, male gender, work-related kneeling or squatting, stairs walking, and high body mass index (BMI).[72] Knee injury, generalized OA, and varus alignment have also been identified as risk factors.[75] Apart from gender, risk factors for degenerative meniscal tears resemble those of knee OA.[76] Tears categorized as degenerative are typically horizontal, i.e., the superior and inferior meniscus surfaces are separated apart, or they have two or more tear patterns (complex) (Figure 2). Complex tears are the most common of all meniscal lesions and are frequently seen in combination with other degenerative changes within the knee joint.[56] Medial meniscal tears are more common than lateral tears.[77] In the middle-aged and elderly population, tears in the medial meniscus account for more than two-thirds of the total number.[1]

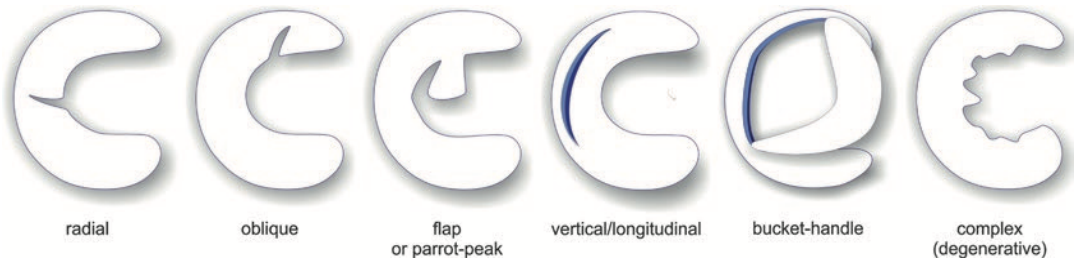

Figure 2. *Meniscal tear patterns (From Piedade et al.[74] with permission from Springer Nature)*

Degenerative meniscal tears - An early sign of knee OA

The prevalence of degenerative meniscal tears identified on magnetic resonance imaging (MRI) ranges from 19% in women aged 50 to 59 years to over 50% in men aged 70 to 90 years.[1] The prevalence is higher in men in all age groups, e.g., 32% in the age group of 50 to 59 years compared to 19% in women.[1] In individuals with concomitant knee OA the prevalence is even higher, up to 70%-90%, and increases with higher OA severity grade.[4,78]

Meniscal tears have been suggested as a direct cause of knee symptoms,[79] and there is no doubt that some individuals experience severe pain and functional limitations.[2] Yet, in population-based studies, the majority of meniscal tears are found in asymptomatic individuals, questioning the clinical relevance of a tear identified on MRI.[1,80] Although the presence of a tear may increase the risk for future knee symptoms,[79] concomitant OA or other degenerative knee joint changes can confound the direct effect. When accounted for, the effect of meniscal tears on the development of knee symptoms is limited.[78] Mechanical knee symptoms, i.e., the sensation of catching and locking, have further been considered as a signifying feature of meniscal tears.[81] However, typical mechanical symptoms are not specific to those with a degenerative meniscal tear alone.[82-84] Higher frequency and intensity of mechanical symptoms in individuals with concomitant early knee OA indicate that the tear is part of the ongoing OA process.[82]

Meniscal pathology is strongly associated with disease development even in knees with no prior radiographic changes.[5] Degenerative meniscal tears are as such considered a "pre-radiographic" sign of knee OA. Early-stage OA involves pathological processes that, with time, will lead to the destruction of articular cartilage.[85] These processes probably also affect meniscal integrity, making the meniscus susceptible to tear from minor trauma and even normal forces acting on the degenerative structure.[71] A degenerative tear is therefore considered as part of the osteoarthritic process rather than a separate clinical entity. Individuals without established knee OA likely harbor other degenerative knee-joint changes, and the tear is a precursor to more severe OA changes as later evident on radiographs.[5]

Compromised load distribution and overall reduced protective properties of a torn degenerative meniscus likely accelerate further joint degradation. As a consequence of reduced contact area and elevated contact pressure within the joint, stresses on articular cartilage increase.[86] Indeed, meniscal pathology is strongly associated also with accelerated knee OA, characterized by a more rapid onset and disease progression.[87] However, the overall number of other risk factors is probably highly determinant for the rate and time of progression to more severe OA changes. In middle-aged individuals with a low number of other risk factors for knee OA, knowledge is lacking with regards to knee OA development and the potential influence of treatment choice.

Diagnosis

Patient history including a detailed description of onset and symptoms, clinical examination, and diagnostic tests guides the diagnosis of meniscal tears. For degenerative tears, a clear recollection of the injury mechanism often lacks as they usually occur without substantial trauma.[57,71] Typical symptoms include knee pain in general, pain when twisting the knee, and pain during stairs walking. Frequently, patients also describe a lack of confidence in the knee.[2,82] Diagnostic tests, such as McMurray`s, joint line tenderness, and Apley`s test are part of the clinical examination with the aim to provide a definitive diagnosis. However, these tests have low accuracy.[88]

Due to the low accuracy of meniscal provocation tests, MRI is used in adjuncts to patient history and clinical examination to verify a clinically relevant meniscal tear. Diagnosis of a tear on MRI is based on the presence of an intrameniscal signal extending to the superior and/or inferior surface of the meniscus and meniscal distortion.[89] The observed increase in signal intensity results from synovial fluid accumulated within a torn or degenerative meniscus.[90] The sensitivity and specificity of MRI for diagnosing a medial meniscal tear are 93% and 88%, respectively.[91] However, the increasing use of MRI is not without controversy. Incidental findings are frequent, and the confirmation of a tear in a degenerative knee has limited implication for treatment.[92,93]

Treatment of degenerative meniscal tears

The goal of treatment is to relieve pain, improve knee function, and prevent or slow further degeneration of the knee joint.[56] In recent decades, APM has been the preferred surgical approach. However, accumulating evidence has questioned the clinically relevant benefit over non-surgical treatment, and exercise therapy is now recommended as first-line treatment for symptomatic degenerative meniscal tears.[94]

In addition to APM and exercise therapy, meniscal repair is a treatment option for meniscal tears. Younger patients with traumatic tears in the vascularized zone are candidates for meniscal repair.[73] However, repair of meniscal tears is typically not an alternative for middle-aged and elderly patients due to tear type and localization.[73]

Surgical treatment

The history of meniscal surgery dates back to 1883.[95] As the meniscus was considered functionless, total meniscectomy prevailed as the procedure of choice and remained the widespread treatment of meniscal tears for almost a century.[57] During the 1980s, the paradigm changed from total to partial meniscectomy. The change was likely due to an increased understanding of the function of the menisci and improved surgical techniques following the introduction of arthroscopy.[56] APM involves excision of only diseased unstable tissue while preserving a stable rim of meniscal tissue.[57] Numerous observational studies reported positive outcomes following the procedure,[96-99] and the likelihood of developing radiographic OA was also lower compared to total excision.[100]

Arthroscopic procedures for degenerative knee diseases increased steadily in the 1990s.[14] The effect was first questioned following the seminal placebo-controlled trial by Moseley et al. in 2002.[101] They demonstrated no difference between arthroscopic lavage or arthroscopic debridement (including resection of the meniscus) compared to placebo surgery in patients with knee OA. Six years later, Kirkley et al. found equal benefit of debridement and exercise therapy compared with exercise therapy alone.[102] In response to the evidence, a marked shift occurred in the indication for knee arthroscopy. The number of partial meniscectomies increased, whereas debridement for knee OA decreased.[13,14] In England, the number of knee arthroscopy for OA declined by 80% from 2000 to 2012. In the same period, the number of partial meniscectomies increased by 230%.[103]

In middle-aged patients with degenerative meniscal tears, several high-quality randomized trials with follow-ups up to five years have more recently shown clinically relevant improvements following both exercise therapy and APM, or a combination of both. No additional benefit from surgery compared to exercise therapy alone has been found for patient-reported pain or function, neither in patients with concomitant knee OA[20,22,23,27,28,30,31] nor in patients with no or only minor radiographic OA changes.[24,26,32] Furthermore, the substantial placebo effect of the arthroscopic procedure has been shown in the expertly executed placebo-controlled trial by Sihvonen et al.[21,29,33] The accumulating evidence questioning the clinically relevant effect over non-surgical treatments has led to clinical guidelines refraining to recommend APM for degenerative meniscal tears.[94,104]

Exercise therapy

Exercise is strongly recommended for patients with knee degeneration,[105] with positive effects on pain and function.[106] Patients with symptomatic degenerative meniscal tears presenting to clinical practice have reduced knee muscle strength and functional performance.[3] Exercise therapy aims to address these deficits, and muscle strengthening and neuromuscular exercises should be the cornerstones of exercise interventions.[107]

The first trial comparing exercise therapy alone with APM for degenerative meniscal tears was published in 2007.[20] In subsequent years, five different randomized trials studied the efficacy of exercise therapy for degenerative meniscal tears.[23-26,28] In these studies, the intervention period ranged from six to 12 weeks, exercises were performed two to three times per week, and at least one of the weekly sessions was supervised by physical therapists in an outpatient clinic. The participants also performed additional exercises at home or in a gym once or twice weekly. All programs focused on strengthening exercises, and the majority included exercises targeting neuromuscular control.

Improvements in knee muscle strength may be one of the underlying mechanisms of pain relief and reduced activity limitations.[108,109] The exact application of training volume and intensity to improve knee muscle strength remains unknown for degenerative meniscal tear patients. For healthy adults, intensities of at least 60% of the maximum weight a person is able to lift (one-repetition maximum) are recommended to achieve strength improvements.[110] Higher exercise intensity (>70% of one-repetition maximum) is further suggested as more effective than exercising at lower intensities in musculoskeletal rehabilitation. However, when used as a therapeutic modality in individuals with knee pain, gradual introduction and progression are important, so the patient ameliorates rather than exacerbates symptoms and becomes accustomed to handling heavier loads.[111] This can be achieved through periodization with regards to varying volume and intensity, which is also optimal to facilitate neural and muscular adaptions.[112] Applying the principles of progressive overload and periodization of volume and intensity has shown to be well tolerated by degenerative meniscal tear patients. Pain levels during the session are acceptable, and knee muscle strength improves significantly following 12 weeks of intervention.[26,107,113]

Neuromuscular exercises target the ability to produce controlled movement through coordinated muscle activity (neuromuscular control) and the ability of the joint to remain stable during physical activity (functional stability).[114] Neuromuscular dysfunctions,

including altered muscle activation patterns and reduced functional performance, are observed in middle-aged individuals with degenerative knee diseases.[115,116] The exercises are performed in functional weight-bearing positions and involve multiple joints and muscle groups. Emphasis is on the quality of movement and maintaining alignment between the knee, hip, and ankel.[114] Hence, these exercises address strength, proprioception, and balance. Neuromuscular exercises, alone or in combination with resistance training, has proven effective in improving functional performance in degenerative meniscal tear patients.[26,117]

The potential influence of treatment on knee OA risk

Good muscle function may be a protective factor for knee OA.[47] Clinically relevant improvements in knee muscle strength have been observed after twelve weeks of exercise therapy, with statistically significantly better improvements compared to APM up to 12 months following treatment.[26,113] Following partial meniscectomy, muscle strength may actually decrease due to surgery-induced trauma and further disuse.[118,119] Reductions in knee extensor strength as long as four years post-surgery have been observed.[118] However, no study has evaluated between-group differences at follow-ups longer than 12 months. There are indications for the clinical relevance of sufficient muscle strength in the degenerative meniscal tear population. Higher muscle strength four years after partial meniscectomy is associated with less severe OA changes 11 years later,[49] and knee extensor muscle weakness is a risk factor for knee OA development in women with meniscal pathology.[48]

On the other hand, APM has been established as a strong risk factor for incident radiographic OA and worsening cartilage damage.[43,120] Furthermore, APM is associated with a threefold increase in the risk for knee replacement surgery.[121] While the results from these observational studies provide valuable information, it is difficult to disentangle whether the increased risk is attributed to the initial meniscal injury, the surgical procedure, or both.[122]

Randomized controlled trials comparing surgical and non-surgical interventions are necessary to assess causal relationships between meniscal injury, partial meniscectomy, and OA development. Six out of eight randomized trials comparing APM with exercise therapy or sham surgery have reported results on progression or development of radiographic knee OA (Table 1).[22,24,30-33] In general, none or only minor between-group differences are reported at follow-ups after two and five years.

Table 1. Randomized controlled trials of patients with degenerative meniscal tears with radiographic outcomes

Author	Interventions	n	OA grade	Age	BMI	Follow-up	Cross-over[a]	Results
Herrlin (2012)	APM + ET versus ET	96	Ahlbäck[b] 0-1	55	25.8	5 years	27%	Prog. (Ahlbäck): 5% (APM) 4% (ET)
Yim (2013)	APM + ET versus ET	108	KL[c] 0-1	56	25.7	2 years	0%	Incidence (KL): 4% (APM) 6% (ET)
Katz (2020)	APM + ET versus ET	351	KL 0-3	58	30.2	5 years	38%	TKR incidence: 9% (APM) 5% ET
Sonesson (2020)	APM + ET versus. ET	150	Ahlbäck 0	54	-	5 years	29%	Prog. (KL)[d]: 60% (APM) 37% (ET)
Berg (2020)	APM versus ET	140	KL 0-2	50	26.3	5 years	20%	Incidence (KL): 16% (APM) 15% (ET)
Sihvonen (2020)	APM versus sham surgery	146	KL 0-2	52	27.5	5 years	11%	Prog. (KL): 72% (APM) 60% (sham)

OA=Osteoarthritis; BMI=Body mass index; APM=Arthroscopic partial meniscectomy; ET=Exercise therapy; Prog=Progression of one grade or more on the radiographic classification system; KL=Kellgren and Lawrence classification system; TKR=Total knee replacement; [a]Cross-over rate from exercise therapy or sham surgery to APM; [b]Ahlbäck classification of knee osteoarthritis (0-5, higher is worse); [c]Kellgren and Lawrence classification system (0-4, higher is worse); [d]Results for as-treated population

Outcome measurements

Selection of appropriate outcome measurements is crucial when designing clinical trials as recommendation of a specific treatment can be made based on the results.[123] Therefore, outcome measures need to be relevant and important to decision-makers, patients, and clinicians.[124] The development and use of core outcome sets help to achieve this. A core outcome set is an agreed set of outcomes (domains) that should be measured and used in all clinical trials of a specific condition.[123]

The Outcome Measures in Rheumatology (OMERACT) and The Osteoarthritis Research Society International (OARSI) has developed a core domain set for clinical trials in knee OA.[125] Five domains are considered mandatory: (i) pain, (ii) physical function, (iii) quality of

life, (iv) patient global assessment of the target joint, and (v) joint structure. These domains align with the International Classification of Function (ICF) common framework of functioning and health.[126] Pain, physical function, quality of life, and patient global assessment correspond to the ICF areas of *Activity and participation*, whereas joint structure corresponds to ICF *Body function and structure*.[126,127]

The joint structure domain in the OMERACT-OARSI core outcome set refers to imaging (such as radiography or MRI) reflecting changes in joint structure.[125] These pathophysiological manifestations are measures of *Body structure* impairments according to the ICF model.[126,127] Plain radiography is the diagnostic gold standard for knee OA despite the advent of modern imaging technologies such as MRI.[128] The joint structure changes covered by radiography are joint space narrowing (JSN) and osteophytes.[129] Assessment of JSN has been demonstrated to fulfill the OMERACT validity requirements (Filter 2.0) and is specifically recommended as an outcome in clinical trials.[129,130]

Patient-reported outcomes assessing pain, physical function, and quality of life are increasingly recognized by clinicians and regulators as essential for evaluating the effectiveness of interventions in clinical trials.[131,132] Several disease-specific patient-reported outcome measures are used in the literature to assess patient-perceived pain and knee function after treatment of meniscal injuries.[133] These disease-specific outcomes generally focus on *Activity* limitations according to the ICF framework,[126,134] whereas aspects of participation in life activities typically are less represented. Thus, for a broader assessment of the impact of the disease they are often complemented by generic measures of general health perceptions and overall quality of life.[135] The domain physical function is particularly complex to assess because it represents multi-dimensional constructs.[136] Physical function can be classified as *Activities* according to the ICF framework and is related to the execution of a task or action.[126] Patient-reported questionnaires assess what individuals perceive they can do, whereas objective assessment by means of functional performance tests evaluates what they actually can do.[137] Performance-based methods may also be better at distinguishing between pain and function.[136] Therefore, they are seen as an essential complement to patient-reported outcomes when assessing physical function.

A specific pathophysiological manifestation relevant for clinical trials evaluating treatment efficacy in an early knee OA population is muscle strength. Muscle strength weakness can be classified as impairment of *Body structure* according to the ICF model[126,138] and is vital to

include as it may be a potentially modifiable risk factor for knee OA development.[47-49] It is further well known that individuals with established knee OA have significant muscle impairments that affect physical function.[139] Inclusion of knee muscle strength measurements thereby enables assessment of whether or not the interventions under study affects one of the pathophysiological consequences of degenerative meniscal tears.[127]

Differential treatment response – Do subgroups exist?

The existence of subgroups within the overall degenerative meniscal tear population that can benefit from APM is a widely held content.[140] However, secondary analyses from randomized controlled trials have failed to demonstrate additional benefit of APM for subgroups of patients commonly argued as optimal candidates for surgery, e.g., patients with meniscal symptoms, failure of initial conservative treatment, or acute onset of symptoms.[26,29,104,141,142] Furthermore, multivariable prognostic prediction models based on preoperative clinical factors proposed as pivotal indications for arthroscopy have failed to identify subgroups with favorable outcome after meniscal surgery.[140] Considering the overwhelming evidence of treatment equality with exercise therapy on patient-reported pain and function, emphasis should be on identifying prognostic factors irrespective of treatment approach.

Identifying degenerative meniscal tear patients who have poor prognosis remains an unsolved puzzle. In a survey carried out on orthopedic surgeons, the percentage of correct predictions of patients who would benefit the most (responders) or least (non-responders) from APM or exercise therapy was similar to the prediction expected by chance alone.[143] The predictions were made based on actual patient profiles from a randomized controlled trial.[28] However, variables known to be prognostic for long-term outcomes in the knee OA population, such as muscle strength, objective knee function, and psychological factors, were not considered.[144-147] Thus, broader and improved knowledge on variables influencing treatment outcomes in patients with degenerative meniscal tears is necessary. Establishing prognostic factors would facilitate early identification of patients at risk of poor outcome and identify potential targets for early interventions.

Thesis aims

The overall aim of this thesis was to evaluate long-term (five-year) consequences of APM compared to exercise therapy in middle-aged patients with degenerative meniscal tears and no or minimal radiographic knee OA.

The specific aims were as follows:

I. To evaluate progression of individual radiographic OA features and development of knee OA five years following APM compared to exercise therapy (Paper I)

II. To evaluate changes in patient-reported pain and knee function five years following APM compared to exercise therapy (Paper I)

III. To identify patient-reported pain and knee function trajectories over five years in patients with degenerative meniscal tears, and explore prognostic factors associated with different trajectories for difficulty participating in sport and recreation (Paper II)

IV. To evaluate longitudinal knee muscle strength changes (three and twelve months, and five years) following APM compared to exercise therapy (Paper III)

V. To examine quadriceps and hamstrings muscle strength at baselines as risk factors for knee OA progression over five years following APM and exercise therapy (Paper III)

Material and methods

The Odense Oslo Meniscectomy versus Exercise (OMEX) trial

The OMEX trial was designed as a randomized controlled trial with two parallel intervention groups. One hundred and forty participants were randomized to treatment with APM or exercise therapy. The participants were recruited at Oslo University Hospital (October 2009 to April 2011) and Martina Hansen Hospital (May 2011 to September 2012). Due to poor influx of knee pain patients at the first site, the recruitment process was taken over by Martina Hansen Hospital (from patient number 54), which had a higher knee patient volume.

Figure 3 describes milestones and publications originating from the OMEX trial.[3,26,32,107,113,148-150] The three papers included in this thesis are based on the participants included in the randomized controlled trial. Paper I included all participants from the OMEX trial with complete baseline and five-year follow-up data (n=120 radiographic outcomes, n=119 patient-reported outcomes). Paper II included all 140 participants and was based on patient-reported outcomes from baseline, three-, 12-, 24-month, and five-year follow-ups. Paper III was based on muscle strength data from all 140 participants (baseline, three- and 12-month, and five-year follow-ups) and radiographic data from 120 participants (baseline and five-years).

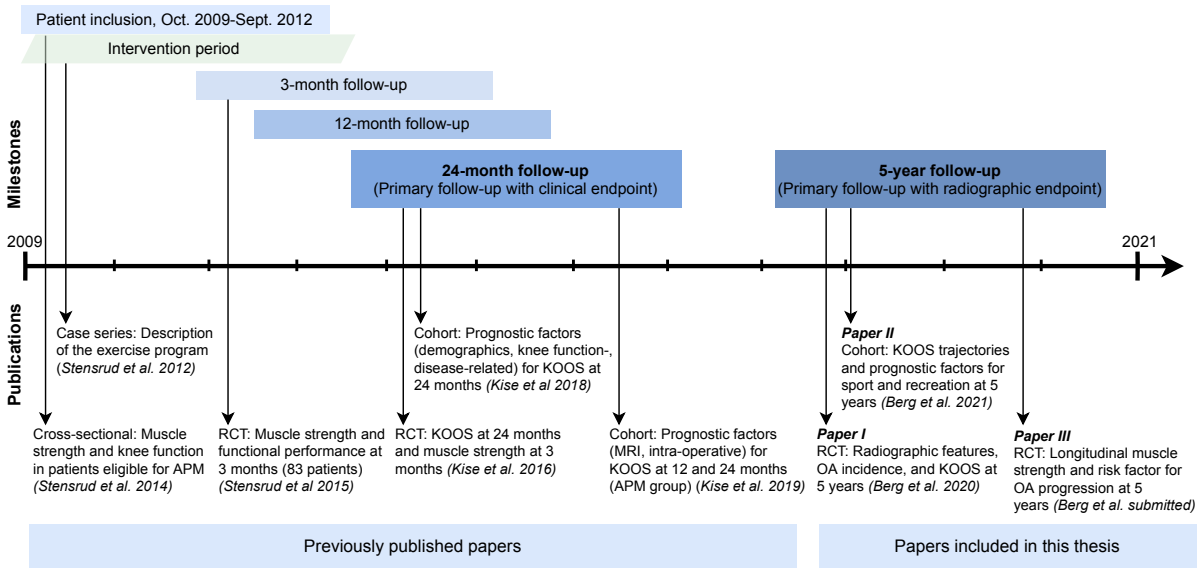

Figure 3. *Timeline illustrating milestones and publications originating from the OMEX trial*

Ethics

The OMEX trial was registered at ClinicalTrials.gov (NCT01002794) and conducted according to the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics of South-East Norway (ref-nr 2009/230) approved the trial. Project amendments for the five-year follow-up were applied and approved by the regional ethics committee. All participants signed informed written consent before enrollment and before participation in the five-year follow-up.

Participants

All included participants had non-traumatic unilateral knee pain lasting for over two months and an MRI-verified degenerative meniscal tear. A degenerative meniscal tear was defined as an intrameniscal signal penetrating one or both surfaces of the menisci. Further inclusion criteria comprised age between 35 to 60 years, at most grade 2 radiographic changes according to the Kellgren and Lawrence (K&L) classification, and able to participate in exercise therapy. The participants also had to be considered eligible for arthroscopy by one of two orthopedic surgeons based on patient history, physical examination, and MRI findings. Exclusion criteria were acute knee trauma, ligament injury, locked knee, and surgery in the index knee during the previous two years.

Out of 341 patients assessed for eligibility, 140 were randomized to APM or exercise therapy (Figure 3). Of the 70 participants in each treatment group, 60 completed the exercise therapy program and 64 completed APM. One hundred and twenty participants (86%) underwent radiographic assessment at five years (58 in the exercise group and 62 in the APM group). Fourteen participants (20%) from the exercise group had crossed over to receive APM two years after inclusion, but there were no new cross-overs between the two- and five-year follow-up.

Power calculation

The sample size of 140 participants in the OMEX trial was based on the two-year primary endpoint, the change in $KOOS_4$ from baseline to two years.[26] The trial was originally powered to detect a 10 point difference with a standard deviation of 15, an estimated dropout

rate of 15%, and a 20% cross-over rate. No a priori power calculations were performed for the five-year follow-up.

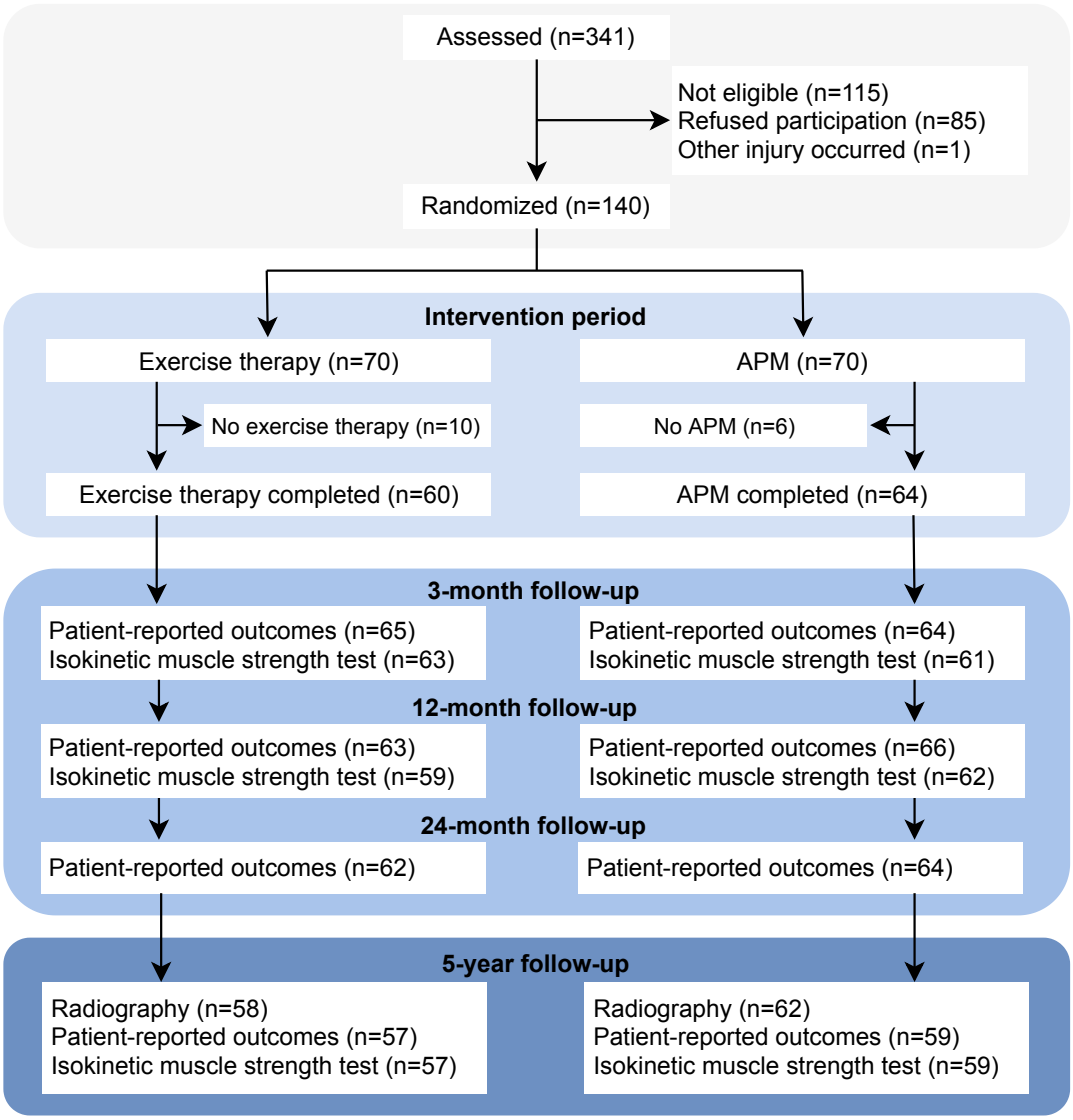

Figure 4. *Flowchart of the OMEX trial*

Randomization

The participants were randomized in a 1:1 ratio, stratified by gender in blocks of eight. An independent statistician determined the computer-generated randomization sequence. The allocations were kept in sequentially numbered opaque envelopes and concealed from the surgeons who enrolled and assessed the participants. The participants contributed baseline data before they were randomly allocated to APM or exercise therapy.

Data collection

Baseline data were collected before randomization, including radiographic and MRI assessments. Baseline and follow-up assessments at three and 12 months were performed during clinic visits. Patient-reported outcomes were collected, and the participants performed isokinetic strength tests and functional performance tests. The two-year follow-up included patient-reported outcomes only, collected by mail. Radiographic assessment was repeated at five years, as well as muscle strength testing and patient-reported outcomes.

Experienced test assessors carried out the clinical testing following detailed test protocols. At three and 12 months, the assessors were blinded to group allocation. To preserve blinding, the participants wore long pants or neoprene sleeves to hide surgical scars.

Radiographic assessments were carried out at the recruiting hospital (baseline) and a private radiology clinic (five-year) using the same standardized protocol.[151] Weight-bearing anterior-posterior radiographs were obtained without fluoroscopic guidance. The protocol further included 10º caudal x-ray beam angulation centered on the back of the knees at the level of the joint line and the use of a Synaflexer (Synarc, Newark, CA) positioning frame. Participants were positioned with the thigh, patella, and pelvis flush with the frame to achieve a fixed knee angulation of approximately 20º. The inner aspects of the foot and heel were pressed against the V-shaped support on the base of the frame, resulting in 5º external foot rotation (Figure 5).

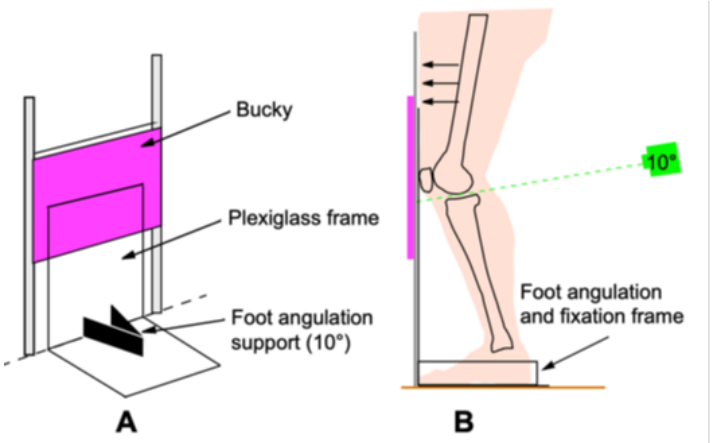

Figure 5. *Fixed-flexion radiography with the Synaflexer frame, (A) illustrating the foot angulation and (B) illustrating the positioning of the participants and x-ray beam angulation (From Charles et al.[152] with permission from Elsevier)*

Interventions

The interventions started as soon as possible after randomization, depending on waiting lists for the arthroscopic surgery. Both interventions have been previously described in detail.[26,107]

APM

The APM procedure was similar in both hospitals, performed by six orthopedic surgeons with at least 10 years of experience. One surgeon at Martina Hansen Hospital performed 38 of the 64 operations (59%), whereas five surgeons at Oslo University Hospital performed between 1 to 15 operations.[26]

The participants were under general anesthesia during the operations, with or without thigh tourniquet, antibiotic-, or antithrombotic prophylaxis. The surgeons used arthroscopes with 30º optics and standard arthroscopic instruments. Normal procedure involved anteromedial and anterolateral portals, with additional portals and a lavage cannula in the cranial recess made if required. Following a diagnostic procedure, including systematic probing of both menisci and inspection of cartilage and ligaments, all unstable meniscal tissue was resected.[26]

The participants were discharged from the hospital on the day of surgery, advised to use crutches until no swelling or discomfort occurred during weight-bearing. Post-operative physical therapy was not part of the intervention, but the participants received written and oral instructions for simple home exercises to regaining range of motion and reduce swelling.[26]

Exercise therapy

The exercise therapy intervention was carried out at the Norwegian Sports Medicine Clinic (NIMI) or Gnist Trening og Helse AS, using the same standardized protocol. The 12-week exercise therapy program was performed for a minimum of two and a maximum of three sessions per week (a total of 24 to 36 sessions). Experienced physical therapists supervised one of the weekly sessions to monitor the quality of the performance and exercise progression.[107]

The exercise therapy program consisted of a 20 minute warm-up on a stationary bike and progressive strengthening and neuromuscular exercises. The strengthening exercises predominantly targeted the quadriceps and hamstrings muscles, were single-leg exercises,

and included both open and closed chain movement. The strengthening exercises were progressed linearly, from high volume and low load initially (2x15 repetitions) to low volume and high load (4x6 repetitions). To further assure progressive overload, the "two-plus rule" was applied, i.e., if the participant managed two or more repetitions over the assigned repetition goal, the load was increased at the next session. The neuromuscular exercises focused on movement quality and knee stability during functional movements. Progression was accomplished by introducing more challenging tasks (e.g., changing the support surface or velocity of the movement), guided by the clinician's evaluation of movement quality and control.[107]

To assess compliance with the exercise program, the participants filled in exercise diaries. Compliance was defined based on the total number of exercise sessions completed out of 24 sessions. Completing at least 19 sessions (≥80%) was predefined as satisfactory compliance, and less than 19 session (<80%) as poor compliance.

Outcomes

The primary outcome in Paper I was progression of individual radiographic features assessed by the OARSI atlas. A total radiographic score was also calculated based on the individual radiographic features. Additional outcomes in Paper I included incidence of radiographic and symptomatic knee OA, medial fixed joint space width (fJSW), and the five individual Knee injury and Osteoarthritis Outcome Score (KOOS) subscales. The KOOS was the outcome in Paper II, with separate trajectory analyses performed for the five individual subscales and $KOOS_4$. For Paper III, isokinetic muscle strength was the primary outcome.

Radiographic outcomes

Two experienced radiographic readers independently graded all radiographs according to the OARSI atlas and K&L classification, blinded to group allocation and clinical data. Baseline and five-year radiographs were read paired and unblinded to time sequence. In case of disagreement for the individual radiograph features or K&L grade, the interpretation of the radiograph was discussed until agreement was obtained.

JSN and osteophytes were scored separately for the medial and lateral compartment according to the OARSI atlas-based scale (0-3, normal to severe changes).[153] Half grades were used when progression had occurred without achieving a full grade on the integer

scale.[154] In Paper I, we defined radiographic progression as an increase of 1 grade or more from baseline to five years for each radiographic feature (dichotomous outcome: Yes or No). For JSN, the medial and lateral compartments were combined due to the low number with lateral progression and increase in JSN grade in either compartment defined as progression. Furthermore, we assessed the total radiographic progression for one knee based on the sum of the individual radiographic features (sum of medial and lateral JSN and osteophyte score).[155] For the secondary objective in Paper III, radiographic OA progression was defined as an increase of one K&L grade or more from baseline to five years (dichotomous outcome: Yes or No).

Knee OA incidence was defined based on the K&L classification.[156] The K&L classification grades OA severity in five grades, from 0 (normal) to 4 (severe), and incidence was defined as emergence of grade ≥2 in knees graded as 0 or 1 at baseline. Grade 2 was defined as a definite osteophyte and possible JSN.[157] Participants with incident radiographic knee OA and experiencing knee pain at least weekly (KOOS question P1) were classified as having incident symptomatic knee OA.[158]

Finally, medial and lateral fJSW measures were done using a semi-automatic method.[159] A computer software automatically delineated the femoral and tibial margins, and one of two readers verified and corrected the computer-determined delineations when necessary. To facilitate measurement of the same location between and within each knee in the serial evaluation, a coordinate system was established based on anatomical landmarks. The measurements were made at $x = 0.250$ (medial) and $x = 0.750$ (lateral), which are the most responsive locations for fJSW measurements (Figure 5).[160]

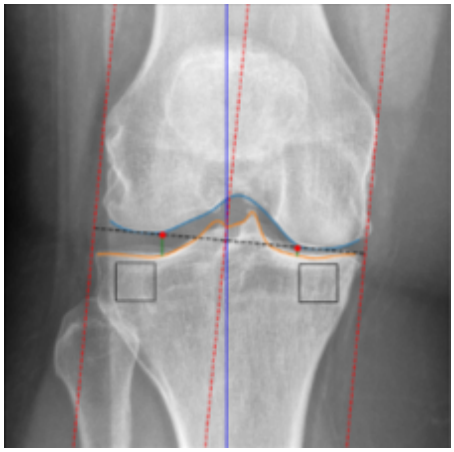

***Figure 6**. Example of fJSW measurement, showing delineation of the femoral condyle and the tibial plateaus, the coordinate system, and measurement of fJSW at x = 0.25 (medial) and x = 0.75 (lateral)*

Patient-reported outcomes

Changes in the five individual KOOS subscales[161] from baseline to five years were included as secondary outcomes in Paper I. The KOOS covers five dimensions that are score separately on a scale from 0 to 100; Pain, other Symptoms, Activities of Daily Living (ADL), Sport and Recreational function (sport/rec), and knee-related Quality of Life (QoL). In Paper II, the absolute KOOS subscale scores at baseline, three, 12, and 24 months, and five years were used to identify patient-reported pain and knee function trajectories. $KOOS_4$ was also included as an outcome in this study, defined as the average score of the subscales pain, symptoms, sport/rec, and QoL. Prognostic factors were further explored specifically for KOOS sport/rec trajectories.

Muscle strength outcomes

Quadriceps and hamstrings muscle strength was assessed at baseline, three and 12 months, and five years using an isokinetic dynamometer (Biodex 6000, Shirley, New York USA). We used the parameters peak torque (Newton meters, N·m) and total work (Joules, J), both normalized for body weight (N·m/kg and J/kg). Changes in normalized quadriceps and hamstrings strength from baseline to each subsequent follow-up were compared between groups in Paper III. The testing protocol included concentric knee extension and flexion at 60°/seconds from 90° knee flexion to full extension. Shoulder and abdominal straps were used to minimize body movements, and the participants were seated in an upright position. A standardized warm-up on a stationary bike and four trial repetitions preceded five recorded maximal test repetitions.

Participants were defined as responders when a change from baseline of at least 15% for quadriceps and at least 20% for hamstrings was detected to facilitate interpretation of the results. The cut-offs were based on the results from test-retest studies.[162-164]

Potential prognostic factors

In Paper II, a range of baseline variables based on current literature[148,165-168] were explored as prognostic factors for different trajectories for patient-reported difficulty participating in sport and recreation.

Demographic variables (gender, age, BMI) were recorded or measured during baseline clinic visits. Further, levels of anxiety and depression were assessed by the Hospital Anxiety and

Depression Scale.[169] Knee function-related factors included: the Global Rating Scale of Perceived Function (0 to 100, worst to best), knee pain assessed with the KOOS pain subscale, quadriceps and hamstrings strength (N·m/kg), three valid and reliable single-leg performance tests, and a measure of physical activity. The three functional performance tests were the one-leg hop, the 6-meter timed hop, and the maximum number of knee bends in 30 seconds.[170,171] As a measure of physical activity, the participants reported participation in sport or exercise and total number of participation hours per week during the last six months before inclusion in the trial (categorized using a cut-off of 150 minutes/week).

The disease-related factors included data derived from pre-intervention MRI scans and radiography. An experienced radiologist re-read all MRI scans and classified meniscal tear pattern and extrusion. Tear pattern was classified according to the ISAKOS meniscal tear classification system.[172] However, as tears with two or more tear patterns may reflect more severe abnormalities, tear pattern was dichotomized as (i) complex tears or (ii) tears with only one tear pattern. The extent of meniscal extrusion was assessed on the coronal image sequence and given in percent (width of extruded menisci relative to the entire meniscal width).[173]

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY) (Paper I) and Stata V.15.0 or later (StataCorp, College Station, TX, US) (Paper I, II, and III). For all three papers, descriptive statistics for continuous variables were presented either as mean and standard deviation (normally distributed) or median and interquartile range (not normally distributed). Categorical variables were presented as frequency and percentages. P-values below 0.05 were considered statistically significant.

Paper I

The primary analyses were performed on the full analysis set[174] (i.e., according to the intention-to-treat principle), including all participants as randomized without imputation of missing data. Between-group differences in progression of individual radiographic features were analyzed using poisson regression with robust standard errors,[175] with separate models for JSN and medial and lateral osteophytes. All models were adjusted for the randomization stratification variable, gender. The same analytic approach was used to compare groups for

progression of incident radiographic and symptomatic knee OA. The results were presented as adjusted risk ratios with 95% confidence intervals (95% CI). The adjusted risk difference was also reported.

Analysis of covariance (ANCOVA) was used to test for between-group differences in change in total radiographic score, medial fJSW, and the five individual KOOS subscales. Gender (randomization stratification variable) and baseline value of the respective outcome were included as covariates.

Per-protocol and as-treated analyses were also performed. For the exercise therapy group, only participants with satisfactory compliance to exercise (≥80% of the total number of exercise sessions) were included in the per-protocol and as-treated analyses (n=32). For the APM group, only participants undergoing APM were included in the per-protocol analysis (n=57), whereas as-treated analysis (n=67) also included participants who had crossed over from exercise therapy to receive APM.

Paper II

In this study, data from the two treatment groups were pooled to improve precision and statistical power. We used group-based trajectory modeling (censored normal model) to identify groups of participants following similar patterns of change for patient-reported pain and knee function from baseline to three, 12, and 24 months, and five years.[176] A two-stage model selection process was used to determine the trajectories. First, the number of trajectories was varied to determine the optimal number of groups. Second, the shape of the trajectories was determined by changing the order of the polynomial. The analyses were repeated in each step, and selection of the optimal model aided by evaluating the Bayesian information criterion (BIC).[176,177] To facilitate interpretability of the results, we required that the smallest trajectory in the selected models included at least 10% of the participants in the sample.

Following model selection, we evaluated additional diagnostics for model fit. The specific statistically oriented criteria indicating good model fit were: (i) average of the posterior probabilities of group membership for individuals assigned to each group exceeding 0.7, (ii) odds of correct classification exceeding 5, and (iii) close correspondence between the estimated probability of assignment and the proportion actually assigned to each trajectory.[177]

The robustness of the results from the primary analyses was assessed in two sensitivity analyses. First, participants with missing outcome data at more than two time-points were excluded (n=7); and second, excluding participants not receiving treatment (n=12).

We used multinomial logistic regression to investigate the association between the potential prognostic factors and the KOOS sport/rec trajectories. The Hosmer-Lemeshow goodness of fit test for multinomial logistic regression was used to evaluate model adequacy.[178] No multivariate modeling was conducted due to the sample size, and we did not adjust for multiplicity given the exploratory nature of this secondary analysis study.[179]

Paper III

Between-group differences in knee muscle strength changes from baseline to three and 12 months and five years were analyzed using intention-to-treat linear mixed models. Linear mixed models were fitted to all outcome variables (normalized quadriceps and hamstrings peak torque and total work) to account for the repeated measures by patient. Participants were included as random effect with random intercept and slopes, except for one outcome variable (hamstrings total work) modeled with random intercept due to convergence difficulties. Time-point, time × treatment interaction, and gender (randomization stratification variable) were included as fixed effects. A main effect for treatment group was not included in the model to adjust for baseline differences.[180]

Potential between-group differences at each follow-up in the proportion of responders for normalized quadriceps (change ≥15% from baseline) and hamstrings strength (change ≥20% from baseline) were tested with the chi-square test.

The relationship between baseline quadriceps and hamstrings muscle strength (N·m/kg) with radiographic OA progression over five years was assessed using a complete-case analysis, i.e., excluding participants with missing outcome data at five years (n=20). Preliminary analysis was performed to test for the interaction between treatment group and muscle strength. No significant interaction was found for treatment × quadriceps interaction (Odds ratio [OR] 1.17, 95% CI 0.85 to 1.61) or treatment × hamstrings interaction (OR 1.29, 95% CI 0.96 to 1.72), consequently data from the two treatment groups were pooled. We conducted separate logistics regression analyses for quadriceps and hamstrings to avoid multicollinearity, with adjustment for gender, baseline K&L grade and KOOS pain scores.

Summary of results

One-hundred and forty participants were included, with a mean age of 49.5 ± 6.4 and BMI of 26.2 ± 4.0. Four participants (3%) had radiographic knee OA (K&L grade 2), 39 (28%) had some radiographic signs of OA but not enough to classified as OA according to the K&L classification, and 97 participants (69%) had no radiographic signs of knee OA (K&L grade 0). Of the participants randomized to exercise therapy, 14 (20%) crossed over to receive APM between three and 20 months after inclusion (mean 8.6 months).

Paper I

Development of osteoarthritis in patients with degenerative meniscal tears treated with exercise therapy or surgery: a randomized controlled trial

Radiographic outcomes

No statistically significant between-group differences were found for progression of individual radiographic features from baseline to five-year follow-up. The adjusted risk ratios (95% CI) for the APM group compared to the exercise group were; 0.89 (0.55 to 1.44) for JSN, 1.15 (0.79 to 1.68) for medial osteophytes, and 0.77 (0.42 to 1.42) for lateral osteophytes. The adjusted between-group difference was -0.02 (95% CI -0.53 to 0.49) for the change in total radiographic score from baseline to five years.

Sixteen percent in both treatment groups developed radiographic knee OA over the five-year follow-up period (risk ratio 1.03, 95% CI 0.46 to 2.30). Two participants in the APM group compared to five in the exercise group developed radiographic knee OA and reported knee pain at least weekly at five years (symptomatic knee OA). For medial fJSW, the adjusted mean change (95% CI) from baseline to five years was -0.50 mm (-0.69 to -0.30) in the APM group and -0.30 mm (-0.51 to -0.09) in the exercise group. The adjusted between-group difference favoring the exercise group was not statistically significant (-0.20 mm, 95% CI -0.48 to 0.09).

Per-protocol and as-treated analyses gave similar results for between-group differences in progression of individual radiographic features and knee OA development. Statistically significant between-group differences favoring the exercise group were found for change in medial fJSW in both the per-protocol (-0.38 mm, 95% CI -0.74 to -0.03) and the as-treated analysis (-0.42 mm, 95% CI -0.76 to -0.08).

Patient-reported outcomes

No clinically relevant between-group differences were found for changes in the five individual KOOS subscales. Both treatment groups had clinically relevant improvements in patient-reported pain and knee function from baseline to five years. The improvements ranged from 13 points (KOOS symptoms) to more than 30 points for KOOS QoL.

Paper II

On a trajectory for success—9 in every 10 people with a degenerative meniscus tear have improved knee function within 2 years after treatment: a secondary exploratory analysis of a randomized controlled trial

Patient-reported pain and knee function trajectories

Three trajectories were identified for patient-reported pain and knee function over five years following treatment for degenerative meniscal tears (Figure 7a-f). The trajectories were generally characterized by similar change patterns and were classified as; (i) *low, minimal improvement* (10%-12% of the participants), (ii) *moderate, gradual improvement* (20%-36%), and (iii) *high, early improvement* (53%-70%).

Sensitivity analyses including only participants who received treatment (n=128) and participants with outcome data from more than two time-points (n=133) also identified three trajectories for all five KOOS subscales and $KOOS_4$. Further, the proportion of participants assigned to each trajectory and the trajectories' shape remained essentially unchanged.

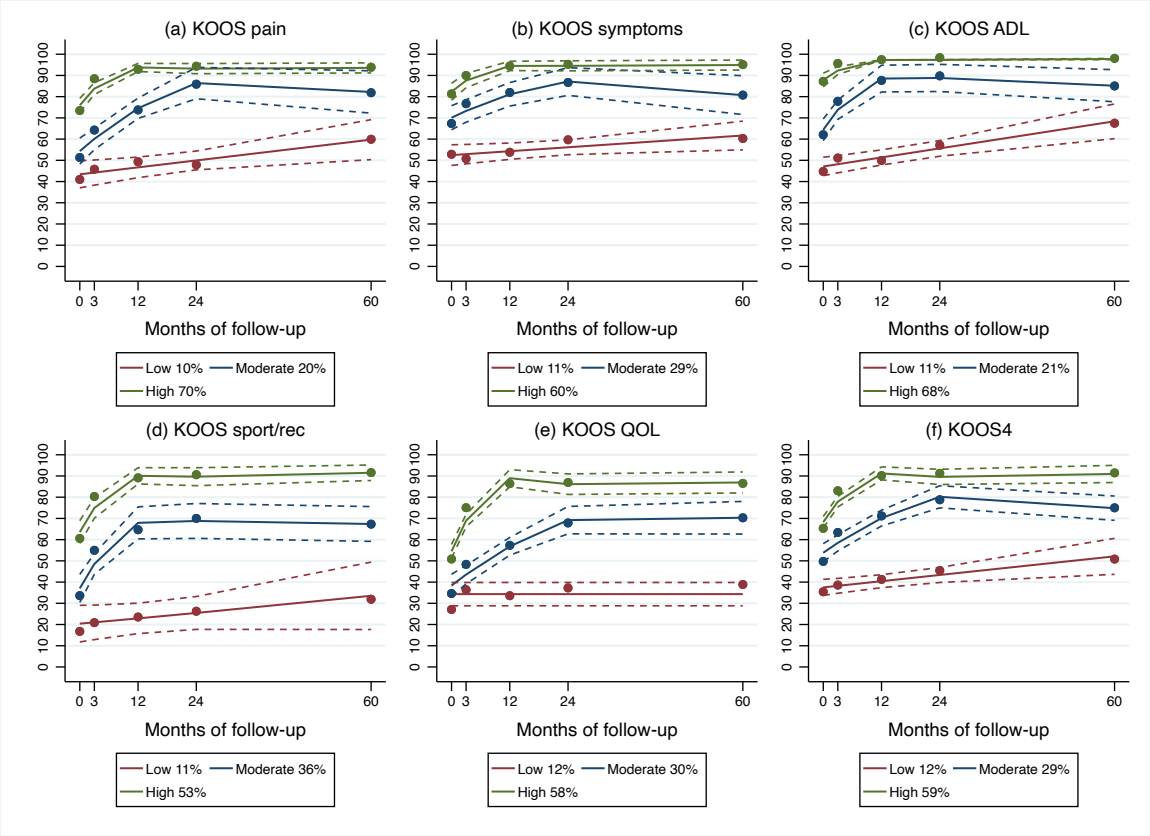

***Figure** 7. Trajectories for KOOS pain (a), symptoms (b), ADL (c), sport/rec (d), QOL (e), and KOOS4 (f). Each point represents the mean KOOS subscale score for each trajectory. Solid lines depict the predicted trajectories, and short-dashed lines represent 95% confidence interval. KOOS=Knee injury and Osteoarthritis Outcome Score; ADL=Activities of daily living; sport/rec=Sport and recreational function; QOL=Knee-related quality of life*

Prognostic factors for KOOS sport/rec trajectories

Several baseline variables were identified as prognostic for patient-reported function in sport and recreation. Higher BMI and poorer mental health increased the risk for belonging to the *low* and *moderate* KOOS sport/rec trajectories compared to the reference category (*high, early improvement*). The *low, minimal improvement* trajectory was further associated with greater knee pain, lower perceived knee function, weaker quadriceps and hamstrings muscle strength, poorer functional performance, higher percentage of meniscal extrusion, and signs of radiographic knee OA. Participants in the *moderate* trajectory also had greater knee pain, lower perceived knee function, weaker quadriceps and hamstrings strength, and poorer functional performance compared to subjects following trajectories characterized by high KOOS sport/rec function and early improvement.

Paper III

Muscle strength and osteoarthritis progression after surgery or exercise for degenerative meniscal tears: Secondary analyses of a randomized trial

Longitudinal knee muscle strength changes

At three months follow-up, statistically significant between-group differences favoring the exercise group compared to the APM group were found for normalized quadriceps (-0.30 N·m/kg, 95% CI -0.40, -0.20) and hamstrings peak torque (-0.10 N·m/kg, 95% CI -0.15, -0.04). Forty-four percent of the participants in the exercise group compared to 16% in the APM group improved normalized quadriceps peak torque ≥15% from baseline to three months (p=<0.001 for between-group difference). For normalized hamstrings peak torque, the proportion of responders (≥20% change from baseline) in the exercise and APM group at three months were 35% and 18%, respectively (p=0.033).

Between-group differences in favor of the exercise group were also found at 12 months (quadriceps: -0.13 N·m/kg, 95% CI -0.23 to -0.03, and hamstrings: -0.08 N·m/kg, 95% CI -0.14 to -0.03). The proportion of responders for normalized quadriceps strength were 42% (exercise group) and 26% (APM group) (p=0.054). The corresponding proportions for normalized hamstrings peak torque were 34% in the exercise and 19% in the APM group (p=0.070).

At five-year follow-up, a statistically significant between-group difference favoring the exercise group was found for change in normalized hamstrings peak torque (-0.07 N·m/kg, 95% CI -0.13 to -0.01). No statistically significant difference was found for changes in normalized quadriceps peak torque between the two treatment groups (-0.10 N·m/kg, 95% CI -0.21 to 0.01).

Risk factor for knee OA progression

Out of 120 participants with complete radiographic data, 65 (54%) were defined as having progressed radiographically over five years. The progression group had a higher proportion of women (43%) compared to the non-progression group (33%). Progressors also had more knee pain at baseline and a slightly higher BMI. Quadriceps muscle weakness at baseline was statistically significantly associated with radiographic progression. For every 0.2 N·m/kg decrease in quadriceps strength the odds of progression increased by 40% (adjusted OR 1.40,

95% CI 1.15 to 1.71). The adjusted odds ratio for every 0.1 N·m/kg decrease in hamstrings strength was 1.14 (95% CI 0.97 to 1.35).

Discussion

Main findings

This five-year follow-up of the randomized controlled OMEX trial comparing APM and exercise therapy as treatments for degenerative meniscal tears showed no strong evidence in support of between-group differences in progression of radiographic OA changes or knee OA development. Both treatment groups showed clinically relevant improvements in patient-reported pain and knee function, but there were no statistically significant or clinically relevant differences between groups. While nine in every 10 participants improved pain and knee function early or gradually over two years, a small subgroup of 10%-12% with severe pain and functional limitations experienced minimal improvement over five years of follow-up. Further, modifiable prognostic factors were identified for sport and recreational function in these middle-aged individuals with no or minimal OA. BMI, mental health, knee muscle strength, and functional performance may be appropriate treatment targets to improve long-term knee function and ability to participate in sport and recreation. Finally, 12 weeks of exercise therapy effectively improved knee muscle strength up to 12 months compared to APM, and quadriceps muscle weakness at baseline was significantly associated with increased odds of knee OA progression over five years. In essence, the principal findings of this thesis support the ongoing shift in treatment strategy for degenerative meniscal tears, recommending exercise therapy over surgical treatment, and advocates a proactive treatment approach for this early knee OA population.

Study designs and methodological considerations

This thesis is based on three papers originating from a randomized controlled trial comparing APM and exercise therapy as treatments for degenerative meniscal tears. The OMEX trial was designed as a superiority trial, with the aim to explore if one treatment was superior to another. The original research question for the primary follow-up with clinical endpoint (two years) was whether exercise therapy was superior to APM for changes in patient-reported pain and knee function. Paper I and III of this thesis include five-year follow-up studies evaluating treatment effects, comparing APM and exercise therapy with respect to; (i) progression of radiographic OA changes, OA development, and changes in patient-reported outcomes (Paper I), and (ii) changes in knee muscle strength (Paper III).

Randomized controlled trial (Paper I and III)

The randomized controlled trial design is recognized as the gold standard for evaluation of therapeutic interventions.[181] A well-designed randomized controlled trial has high internal validity, i.e., the design and conduct eliminate the possibility of bias. Therefore, it is possible to determine whether a cause and effect relationship exists between treatment and outcome.[182]

Random treatment assignment is the best method for balancing measured and unmeasured confounding factors between treatment groups, thus ensuring that average individual characteristics are equally distributed.[182,183] In the OMEX trial, several other measures were taken to guard against additional bias. An independent statistician generated the randomization sequence, and the allocations were concealed from the surgeons who enrolled and assessed the patients, which is necessary to eliminate selection bias.[184] Ideally, patients and healthcare providers should also be blinded after assignment to interventions.[185] However, blinding is not feasible in a trial comparing surgical and non-surgical interventions.[182] The participants' knowledge of group assignment in the current trial may have affected responses to the intervention received.[185] Yet, this is merely a challenge for subjective outcomes and not objective outcomes such as radiographic OA changes. To reduce detection bias for radiographic outcomes at five years, the two outcome assessors were blinded to group allocation and graded all radiographs independently.

A well-designed randomized controlled trial should also have acceptable external validity (generalizability).[182] In the OMEX trial, experienced orthopedic surgeons at high-volume hospitals performed the arthroscopic procedures. Further, experienced physical therapists at one of two sports medicine clinics supervised the exercise therapy intervention. As such, it may be considered an efficacy (or explanatory) trial. An efficacy trial aims to measure the efficacy of an intervention under ideal conditions.[182] In contrast, effectiveness (or pragmatic) trials are designed to measure the effectiveness of an intervention in routine clinical practices.[186] Effectiveness trials aim to maximize external validity, but the internal validity is usually lower. However, the distinction between efficacy and effectiveness trials is not a strict dichotomy, and the OMEX trial may be considered to lie somewhere along the spectrum between these two designs.[182]

The main issues that can affect external validity are the trial setting, selection and characteristics of the patients, and how treatment protocols compare to routine clinical

practice.[187] The participants were included in a standard clinical setting, referred by their general practitioner, and were considered eligible for both exercise therapy and surgery. The three-year recruitment period at two orthopedic departments may indicate strict inclusion criteria, which could be a threat to external validity.[187] However, there was no parallel inclusion at the two sites. The inclusion rate was considerably higher (4.9 patients per month) at the second hospital. Regarding patient characteristics, our findings are applicable to middle-aged patients with no or minimal radiographic knee OA. Middle-aged patients with little to no OA (K&L grade 0-1) have been considered the typical patient group who might benefit the most from APM. Proponents of the procedure still suggest surgery after failed non-operative management of short duration for these patients.[188] Therefore, comparing APM and exercise therapy for this specific patient population is highly clinically relevant, with the potential to alter clinical decisions and treatment recommendations. As such, the trial meets the needs of decision-makers, which ultimately is of most use to clinicians and patients.[182] Finally, the two interventions were reflective of standard clinical care. Standard arthroscopic equipment and surgical techniques were used,[26] and the exercise therapy program is readily available and easy to adapt in clinical settings.[107]

Reporting of the randomized controlled trial (Paper I and III) followed the Consolidated Standards of Reporting Trials (CONSORT) statement.[189] The CONSORT comprises a checklist of essential items to include in the reporting of parallel-group randomized trials, and adherence to this 25 item checklist facilitates clarity, completeness, and transparency of reporting.[189,190] Even though CONSORT advises on reporting study interventions (item 5 in the checklist), adhering to the more recently developed extension, the Template for Intervention Description and Replication checklist and guide,[191] when reporting the two interventions would have strengthened the study. Nevertheless, the description of the interventions, including the more detailed description in previous publications,[26,107] should be sufficient to allow replication by other researchers.

Explorative study (Paper II)

Paper II was a secondary explorative analysis study including all 140 participants from the randomized controlled trial. An exploratory study differs from a confirmatory study in that there are no prespecified hypotheses.[179] The basis for this study was the observed heterogeneity in treatment response. The results from Paper I and previous patient-reported follow-up data[26] raised the research question of whether subgroups of individuals following

distinct change patterns could be identified and if baseline variables were prognostic for worse outcome. In this study, data from the two treatment groups were pooled to improve precision and statistical power. Combining the two treatment groups was considered appropriate as no group differences between APM and exercise therapy has been detected for changes in patient-reported outcomes in the OMEX trial.[26,32]

The reporting of the secondary analysis study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline to ensure transparent and accurate reporting.[192] The STROBE statement is a checklist of items that should be addressed in observational studies.[193] The checklist was developed because reporting of study design, analysis, and results in observational studies is often inadequate,[194] which hampers the assessment of study strength and weaknesses and interpretation of generalizability.[192] The STROBE checklist was used because data from the two treatment groups were pooled and considered one cohort. The study also aimed at using baseline factors to predict future outcome, which is a typical feature of a prospective cohort study: following a group of patients over time, collecting health-related variables at the beginning of the time-period and assessing relations between these variables and later recorded outcomes.[181]

Participants

Patients referred by their general practitioner with knee pain lasting over two months and an MRI-verified degenerative meniscal tear were considered eligible for inclusion. As incidental MRI-findings are highly prevalent,[1] all patients were thoroughly examined by one of two orthopedic surgeons to confirm clinical signs and symptoms consistent with a degenerative tear. Out of 341 patients assessed for eligibility, 85 (25%) refused to participate in the study. At the time of recruitment, APM was the usual treatment for degenerative meniscal tears, and the majority (52 participants, 61%) who refused participation were not willing to undergo exercise therapy. Besides, 17 participants (20%) refused to undergo APM and 16 participants (19%) reported other reasons (distance to trial locations the most frequent).

The OMEX trial participants were middle-aged (49.5 years old), slightly overweight (BMI 26.3), and 97% did not have radiographic knee OA. Compared to similar high-quality randomized trials, only one study included participants solely without radiographic knee OA but of slightly higher age (mean 56.3 years old).[24] The remaining trials have included a higher proportion with concomitant radiographic OA (from 18% to 70%), somewhat older

participants (mean age 52 to 58), and generally with a slightly higher BMI (from 26 to 30).[22,28,30,31,33]

The participants presented KOOS subscales scores indicating moderate to severe pain and functional disability at the time of inclusion. Compared to age-specific reference data,[165] the participants' mean subscale scores were approximately 20 points worse for KOOS symptoms and ADL, 30 points worse for KOOS pain, and more than 40 points worse for KOOS sport/rec and QoL. Pain and functional impairments of similar severity have been reported in other randomized trials and cohort studies using the KOOS,[2,27,195] indicating the included participants were representative of the typical degenerative meniscus population.

Missing data

Of the 140 included participants, 120 (86%) underwent radiographic assessment at five years. Participants lost to follow-up did not differ from those included in the analyses, except for a higher proportion with meniscal extrusion among patients lost to follow-up (80% versus 56%). As a rule of thumb, less than 5% loss to follow-up leads to little bias, whereas loss to follow-up of more than 20% poses a threat to the validity of the results. However, more important than the overall loss to follow-up rate is the comparative loss rates in the randomized groups.[196] In the OMEX trial, the number of participants lost to follow-up did not differ appreciably between the two treatment groups (12 participants in the exercise group and 8 in the APM group).

The rate of missing data was also acceptable for clinical outcomes. The number of participants completing patient-reported outcomes was 129 (92%) at three and 12 months, 126 (90%) at 24 months, and 119 (85%) at five years. For isokinetic muscle strength tests, the numbers at three-, 12-month, and five-year follow-ups were 124 (89%), 121 (86%), and 116 (83%), respectively.

Cross-overs

A particular challenge in trials comparing surgical and non-surgical interventions is the possibility of one-way cross-over since once a patient has had surgery it cannot be undone.[197] Yet, in the OMEX trial cross-over from the APM group to exercise therapy was predefined as receiving at least 18 sessions of exercise therapy instructed by a physical therapist. Five participants allocated to APM received passive physical therapy only, and none were defined

as cross-overs. Out of the 70 participants randomized to exercise therapy, 14 participants (20%) crossed over to receive APM at a mean of 8.6 months after inclusion. Four of these participants had declined exercise therapy and two had low compliance to the exercise program (<80% of the total number of exercise sessions). In comparison, six participants treated with APM underwent another surgical procedure (APM, high tibial osteotomy, or total knee replacement). It is essential to compare the cross-over rate to arthroscopic treatment failure,[94] although patients who are initially treated non-operatively probably are more likely to seek additional treatment (surgery) when symptoms persist.

Higher cross-over rates have been reported at five years in other randomized trials comparing APM and exercise therapy. The study by Herrlin et al.[22] and Sonesson et al.[31] reported a cross-over rate of 27% and 29%, respectively. In the study by Katz et al.,[30] 38% crossed over from the exercise group to receive APM. A lower cross-over rate of 11% was reported at five years in the placebo-surgery controlled trial by Sihvonen et al.[33] Of note, 12% in the APM group also reported symptoms severe enough to result in unblinding of the group allocation.[33]

In general, cross-overs have been attributed to persistent pain and functional limitations. To not undermine the randomization process, all participants are included in the analyses as randomized (i.e., according to the intention-to-treat principle). One-way cross-over may introduce bias as the power of the intention-to-treat analysis will be reduced if some participants in the exercise group improved pain and knee function because they received APM.[197] However, participants in the OMEX trial crossed over with no additional benefit compared to those who remained in the exercise group.[26] For radiographic outcomes, the bias may actually work in the opposite direction. If APM indeed is associated with radiographic progression, this effect may not be captured because subjects crossing over to APM are counted in the exercise group.

Outcome measures

This thesis comprised evaluations of radiographic, patient-reported, and muscle strength outcomes. Overall, the included outcomes reflect the OMERACT-OARSI recommended core domains for clinical trials and evaluate the implications of degenerative meniscal tears on the different aspects of the ICF model.[125,126] The following sections discuss strengths and limitations of the outcome measures included in this thesis, with particular emphasis on the

comprehensive radiographic evaluation used to assess potential differences in radiographic OA changes.

Radiographic outcomes

The pre-specified primary aim of the five-year follow-up of the OMEX trial was to describe radiographic changes in knee OA development. In the clinical trial registration (NCT01002794), incident and enlarging marginal tibiofemoral osteophytes were listed as the primary outcome. While OA is defined radiographically as the presence of definite osteophytes, cartilage loss is also a structural hallmark of OA.[85] Cartilage loss is not visible on radiographs but JSN serves as a proxy for loss.[157,198] Using semi-quantitative grades or a quantitative approach for JSN is specifically recommended to monitor OA progression.[157] In Paper I, assessment of JSN was therefore included in addition to osteophyte formation. Assessing JSN separately is also in line with the OMERACT recommendation of imaging measurement instruments in clinical trials.[129] This change was made before scoring the radiographs and analyzing the data.

The OARSI atlas was the primary outcome in Paper I, with progression of osteophytes and JSN evaluated separately in the medial and lateral compartment.[153] Evaluating osteophyte formation and JSN separately may distinguish distinct pathological processes associated with the two interventions.[199] The ordinal grading scale is moderately sensitive to change, and half-grade increments on the integer scale were used to increase the sensitivity.[154,200] However, a low number of participants progressed more than 1 grade. For each individual radiographic feature, grade 1-3 progression was therefore collapsed (dichotomous outcome: Yes or No). Applying a fixed dichotomy to an ordinal outcome typically leads to a loss of statistical power.[201] Consequently, the reduced statistical power caused an increased risk of Type II error. A sum score of the individual OARSI grades was further calculated to reflect the affected knee's total radiographic changes. Through being continuous and emphasizing both osteophytes and JSN, assessing changes in the total radiographic score to a larger extent allowed the opportunity to detect between-group differences compared to only a crude radiographic scale (such as K&L).

A particular strength of Paper I is the inclusion of a location-specific computer-assisted quantitative measure of medial fJSW.[160] Alternatives for measuring the distance between the adjacent femur and tibia margins on plain radiographs includes the interbone distance

measured at the local minimum or the mean width.[202,203] Surface area measurements are generally considered less sensitive to change as normal joint space may be included.[202] Minimum joint space width (JSW) has traditionally been quantified by a reader visually determining the minimum distance between the projected femur and tibia margins. However, this technique suffers from significant inter- and intra-observer variability.[203] Computerized methods have therefore gained favor during recent decades, where digital image analysis software delineates the edges of the joint. The use of fixed locations is further considered more responsive that the traditional measure of minimum JSW.[204] The fJSW method has comparable sensitivity to MRI for detecting OA progression, is highly reproducible and extensively validated.[160,204] As a continuous measure, it also offers the ability to detect joint space loss occurring within the ordinal OARSI JSN grades.[199] Thus, fJSW may to a larger extent reveal progression among participants with an atrophic OA phenotype.

Paper I also included between-group comparison of knee OA incidence. The K&L classification[156] has an extensive historical record and is still the most widely used classification system to define knee OA.[157] To enable comparisons across studies and populations, studies should use the same classification system. However, the K&L classification has received criticism as the grading of OA is highly osteophyte-based and places less emphasis on JSN at the early grades particularly.[157] The assumption that changes in osteophytes and JSN are linear and constant over the course of the disease may be invalid.[205] To overcome this limitation, we used the proposed modification to the K&L classification in which incident disease is defined as the development of a new osteophyte combined with possible JSN (in knees previously graded as either K&L 0 or 1).[157]

The K&L definition of radiographic knee OA was also used to classify participants with symptomatic knee OA. While early radiographic changes (e.g., advancing one grade on the K&L or OARSI scales) are of clinical interest as they represent an important indication of longitudinal incident disease,[206] the association with pain and symptoms has been questioned.[207] Knee OA is a clinical syndrome, and including evaluation of clinical findings, such as knee pain, is essential to inform the diagnosis.[208] Yet, defining symptomatic knee OA is a challenge as pain associated with OA fluctuates over time.[209] The definition of symptomatic knee OA usually includes experiencing pain on most days and radiographic features consistent with OA. In Paper I, experiencing knee pain at least weakly was used to define symptomatic knee OA. This information was derived from the KOOS pain subscale

(question P1).[161] There is a lack of validated definitions of symptomatic knee OA, but including the frequently used ACR criteria could have strengthened the interpretability of the study.[210] However, this definition of clinical OA has been suggested to reflect a more severe stage of the disease and capture only every other patient treated in primary care for knee OA.[211,212]

For all the above-mentioned outcomes, standardized radiographs of high quality are essential for valid assessment of longitudinal knee OA changes. In the OMEX trial, the radiographic acquisition protocol dictated weight-bearing, fixed-flexion, anterior-posterior radiographs.[151] The use of a positioning frame further standardized and eliminated variations in knee rotation. This is necessary since osteophytes circumnavigate the tibial plateau or femoral condyle, and knee rotation may cause overlap between the osteophyte and joint margin.[157] Changes in knee rotation may, therefore, lead to non-visualization of previously seen osteophytes (or vice versa) or discrepancy in their apparent size in serial radiographs.[157,213] The radiographic protocol further specified 10º caudal beam angulation to provide correct projection and superimposition of the anterior and posterior tibial margins.[151] However, the beam angulation was not uniform across the time-points for all images and may have caused artificial variation in JSN and fJSW measures in longitudinal assessments.[213] Yet, possible confounding related to variation in beam angle should be equally distributed between the two treatment groups. Estimating the true beam angle from the metal beads on the Synaflexer frame[214] also confirmed no differences between the two groups at either time-point. Accordingly, estimates of between-group differences in medial fJSW should be valid.

Patient-reported outcomes

The KOOS questionnaire was included in Paper I to evaluate patient-reported pain and knee function. The instrument has excellent test-retest reliability in middle-aged patients with meniscal tears and is validated for patients with a wide range of knee complaints, including meniscal tears and knee OA.[161,215,216] Improvement of 8-10 points (on the 0-100 scale) has usually been considered the threshold for minimal important change (MIC).[215] Recently proposed MIC improvement values derived from robust statistical methods confirm these thresholds specifically for patients following meniscal resection, at least in the short-term.[217]

The primary reason for including the KOOS in the OMEX trial was that the psychometric properties of the instrument were established for patients with meniscal tears and knee OA at

the time of trial initiation. Other patient-reported outcome measures used in similar randomized trials include the International Knee Documentation Committee Subjective Knee Form (IKDC),[218] Lysholm,[219] and Western Ontario Meniscal Evaluation Tool.[220] However, these questionnaires had not been subjected to psychometric evaluations in 2009 when this trial started.

In 2014, a Consensus-based Standards for the Selection of health Measurement Instruments (COSMIN) review showed favorable results for reliability and validity of the IKDC compared with the KOOS in middle-aged patients with meniscal injuries peri-operatively and up to six months post-operatively.[133] Accordingly, the authors conclude that the IKDC should be used when assessing patient-reported pain and knee function in patients with degenerative meniscal tears. However, a similar COSMIN review from 2017 concluded that the evidence on measurement properties was incomplete, and a specific patient-reported outcome could not be recommended due to poor methodology.[221] The inclusion of other patient-reported outcomes such as the IKDC may have strengthened the OMEX trial. Yet, in a long-term follow-up study of individuals where the distinction between pain originating from the meniscus or other OA changes often is unclear, the KOOS may be considered favorable as it evaluates both short-term and long-term consequences of a knee injury.[215] Using multiple questionnaires also increases the patient's response burden, potentially leading to lower response rates, reduced completion, and reduced data quality.[222]

The inclusion of only a disease-specific patient-reported outcome measure in Paper I is also a noteworthy limitation. Since the knee-specific KOOS questionnaire focus on pain and knee function within the *Activity* category of the ICF framework,[134] a specific assessment of *Participation* restrictions through generic health questionnaires such as the 36-Item Short Form Health Survey (SF-36)[223] or EQ-5D[224] would have strengthened the study. The SF-36 was included in the two-year follow-up in the OMEX trial, with no statistically significant or clinically relevant between-group differences detected.[26] Finally, performance-based evaluations of knee function were not conducted in this five-year follow-up study, which could have helped portray a more completed picture of physical function. OARSI has endorsed the 30-seconds chair-stand test, 40 meter fast-paced walk test, and a stair-climb test as the minimal core set of performance-based tests for knee OA.[137] While these are recommended for the more severe OA population, they would have complemented patient-

reported assessment of physical function also in this long-term follow-up study of an early knee OA population.

The KOOS was also the outcome in Paper II, with separate trajectory analyses performed for all the five individual subscales and $KOOS_4$ to provide detailed information about limitations and improvements in the various dimensions of patient-reported pain and knee function. $KOOS_4$ was the primary outcome in the primary follow-up with clinical endpoint of the OMEX trial (two-year)[26] and included in this secondary analysis study which also focused on patient-reported outcomes. The composite score was not included in Paper I as it has not been subjected to psychometric validation and is intended for statistical purposes only. In Paper II, prognostic factors were further explored for the KOOS sport/rec subscale. The sport/rec subscale was considered to be of particular relevance for this middle-aged knee pain population without radiographic knee OA. Being able to participate in sport and exercise activities may be integral to achieve lasting pain reduction and maintain good physical function and general health. The KOOS sport/rec subscale has also shown to be more relevant and responsive to detect changes over time in the younger and more physically active patient population, compared to the typically older, more severe knee OA population.[216]

Muscle strength outcomes

An isokinetic dynamometer was used to assess changes in quadriceps and hamstrings muscle strength (Paper III). During isokinetic testing mode, the velocity is kept constant by the dynamometer through the range of motion.[225] Criticism of isokinetic testing refers to the non-functional nature of close kinetic movements. Still, for specific quantification of dynamic muscle function and monitoring changes over time, dynamometry is the recommended modality.[226] Quantification of muscle strength is an important complement to patient-reported knee-function assessment since muscle impairments are the primary underlying cause of functional limitations in knee OA.[139] Muscle weakness may also serve as a potential marker for knee OA development in the long-term. All muscle strength measures were normalized for body weight to facilitate comparison between studies and discriminate among different individuals or populations since body size affects muscle strength.[227]

Isokinetic knee muscle testing is highly reliable for healthy adults and patients with knee OA.[162,228] The testing was performed at a slow velocity (60º/seconds), which is more reliable

than higher velocity (180º/seconds) in patients with early knee OA.[229] A limitation is that three different therapists performed the baseline and follow-up testing, which may have caused variability. However, several practice sessions were conducted, and all testers followed the same detailed test protocol. Proper education and strict adherence to the test instructions are suggested as the most important aspect for reliable and unbiased results of isokinetic muscle strength testing.[226]

Finally, changes of at least 15% for quadriceps and 20% for hamstrings were used to classify responders. These cut-offs were chosen as they are well above the measurement error for isokinetic quadriceps and hamstrings strength tests shown in test-retest studies on healthy individuals (between 5% to 10%).[162,164] It must be acknowledged that variability may be greater in individuals with knee complaints. Therefore, it cannot be excluded that larger improvements may be necessary to indicate real and potentially clinically relevant improvement at the individual level for this patient population.

Sample size

Statistical power is defined as the probability of obtaining statistically significant results when there is a real difference between two groups.[230] No power calculation was made a priori for the five-year follow-up of the OMEX trial since the primary aim of this study was two years. The fixed sample size of 140 participants is a limitation for Paper I given the uncertainty associated with the risk for osteophyte and JSN progression. Estimating the statistical power once a study has been carried out (post hoc power calculation) has little merit. Instead, the confidence intervals of the effect estimates should be used for assessing the practical meaning of the results and is an appropriate indication of the statistical power.[230,231]

Statistics

Paper I

Poisson regression was used to compare the risk of progression of individual radiographic features and knee OA development. Relative risks were estimated, which are preferred over odds ratios as they are considered easier to interpret.[232] Binomial regression can be used to estimate the treatment effect on a binary outcome, but convergence problems are common.[233]

Relative risks were therefore estimated using the poisson regression model with robust error variance.[175] As recommended in the reporting guidelines for randomized controlled trials,[190] the absolute effect (risk difference) was reported in addition to the relative effect (relative risk) to portray a more complete picture of the effect and its implications.

ANCOVA adjusted for baseline value of the outcome (and randomization stratification variable) was chosen to test for between-group differences in continuous outcomes (change in total radiographic score, medial fJSW, and KOOS). Adjustment for baseline was made because of some baseline differences between the two treatment groups, e.g., 0.09 mm for medial fJSW and between 1.1 to 7.6 points on the five KOOS subscales. Irrespective of whether the difference is significant, adjustment for baseline is recommended as follow-up measures are highly related to the baseline value. Even minor differences between treatment groups can have a strong confounding effect.[180]

Paper II

Group-based trajectory modeling was used in Paper II. This specialized application of finite mixture models is designed to identify clusters of individuals (trajectory groups) who have followed a similar developmental trajectory on an outcome.[177] Since the KOOS subscales have a pre-specified range (0-100), a censor normal model was used, which allows for clustering at the scale minimum and maximum.[176] The use of a formal statistical criterion (BIC) in the model selection process discipline and constrain subjective judgment.[177] However, the BIC does not always identify the optimal number of groups cleanly.[176] Group size was therefore also taken into account.

A particular strength of group-based trajectory modeling is the possibility to assess model adequacy through several statistically oriented criteria post-model estimation. The posterior group membership probability measures the likelihood of belonging to each trajectory for a specific individual, summing to 1 across all groups.[176] Individuals are assigned to the trajectory with the maximum posterior group membership probability, and the average of this measure for each trajectory group can be used to judge model adequacy.[176,177] For our models, the average posterior probability of group membership for each trajectory ranged from 0.86 to 0.97, indicating excellent model fit.

Attrition is a challenge in all longitudinal studies. The group-based trajectory model handles missing data by imputing values based on available data points under the assumption that

missing data are *missing at random*.[177] This means that conditional on the observed outcome and covariates, missingness and trajectory group assignments are independent.[234] While there is no test to formally evaluate whether missing data are *missing not at random*, sensitivity analyses were conducted to assess the potential impact of missing data mechanisms.

Multinomial logistic regression, a generalization of binomial logistic regression when the outcome variable is categorical with more than two nominal values,[178] were used to explore associations between baseline variables and KOOS sport/rec trajectory groups. The data were analyzed without multiplicity adjustment as this was an exploratory study without pre-specified hypotheses. This is the recommended approach when hypotheses are generated by the data, but it also means that the results have to be confirmed in future confirmatory studies testing the corresponding hypotheses.[179]

Paper III

The longitudinal data in Paper III was analyzed using linear mixed models. Because the response variable (muscle strength) was repeatedly measured over time (baseline, three and 12 months, and five years), one cannot assume that these responses are independent of one another. Linear mixed models have advantages over traditional linear models as they include a combination of fixed and random effects. The random effects account for correlations between multiple observations per participant.[235] Another significant advantage over traditional linear models, which handles missing data via listwise deletion, is that all subjects are retained in the analyses (only dropping the actual time-point with missing data).[236]

Logistic regression was used to explore baseline quadriceps and hamstrings muscle strength as potential risk factors for the binary outcome of knee OA progression over five years. The models were adjusted for potential confounding factors (gender, baseline K&L grade and knee pain) that may have contributed to muscle weakness and risk for knee OA progression. While we used normalized muscle strength (N·m/kg) in the analyses, arguments have been raised to rather scale muscle strength by controlling for body weight or BMI in the logistic models. Muscle strength does not increase linearly with body mass, which is assumed when dividing strength by mass, because much of the increase in mass is noncontractile tissue.[237] However, the difference in BMI between progressors and non-progressors was relatively small (26.6 kg/m^2 versus 25.3 kg/m^2). Thus, scaling muscle strength by controlling for BMI instead of using normalized muscle strength should not affect the results considerably.

Results

Paper I

Radiographic progression occurred predominantly in the medial compartment, which is expected in individuals with medial degenerative meniscal tears and non-traumatic knee pain.[238] Although comparable proportions progressed in the two treatment groups (risk difference of 4% for JSN [favoring APM] and 7% for medial osteophytes [favoring exercise]), a true difference cannot be ruled out due to the width of the confidence intervals. However, the change in total radiographic score indicates no difference in overall radiographic progression for the affected knee between the two treatments. The confidence interval included a half OARSI grade in either direction, which indeed precluded any potential between-group difference of clinical relevance. Furthermore, comparing changes in medial fJSW, a sensitive and recommended proxy for cartilage loss,[160,204] gave more specific information regarding JSN and the opportunity to identify changes occurring within the ordinal JSN grades. The mean change of -0.20 mm (favoring exercise) and the corresponding 95% CI (-0.48 to 0.09) indicates no relevant between-group difference in JSN. To put the results into context, a mean change of -0.75 mm has been shown for knees transitioning from OARSI JSN grade 0 to 1.[199]

In the per-protocol and as-treated analysis, statistically significant between-group differences were found for medial fJSW favoring exercise therapy. While these analytic approaches may reveal the true treatment effect to a larger extent, e.g., a larger decrease in medial fJSW following APM, they carry different risks of confounding compared to the intention-to-treat approach.[239]

Overall, radiographic progression over five years was modest. Less than 10% of the participants progressed more than 1 grade across the radiographic features. Furthermore, only 16% developed radiographic knee OA over the follow-up period. While reference-based data are scarce, the five-year prevalence of approximately 20% is likely higher than in the general population aged 54 to 56 years (less than 10%),[240] indicating that degenerative meniscal tears are part of the osteoarthritic process. For symptomatic knee OA, only 6% of the participants had radiographic knee OA and concomitant knee pain, whereas 20% reported knee pain without definitive evidence of radiographic knee OA. The correlation between radiographic changes and pain has been suggested to be weak.[207] However, the most methodologically sound study to date found individual radiographic features to be a strong risk factor for the

presence, consistency, and severity of knee pain.[241] Yet, pain was most strongly associated with JSN and the insensitivity of the K&L classification to detect early OA changes causing symptoms may explain the observed discordance between structural changes and symptoms in our study.

In general, the five-year results of the OMEX trial are in accordance with the other randomized controlled trials with respect to between-group differences in radiographic outcomes.[22,24,30,31,33] However, varying incidence and progression rates have been found, likely due to apparent differences in study population, cross-over and retention rate, and radiographic evaluation methods. The most important distinction relates to the proportion of included participants with established knee OA. In the OMEX trial, four participants had radiographic knee OA (K&L grade ≥2) at inclusion. Only one similar trial included participants solely without radiographic knee OA.[24] They found an incidence of 5% (K&L grade ≥2), but the short follow-up time of two years likely explains the low incidence rate.

Of the randomized trials that include a larger proportion with radiographic knee OA, Herrlin et al. found remarkably low radiographic progression rates (two participants in each group).[22] Patients with Ahlbäck grade ≤1 (equivalent to K&L grade ≤3[242]) were included, and the Ahlbäck classification was also used to assess progression. For the Ahlbäck classification, grade 2 requires obliteration of the articular space.[243] Thus, a direct comparison to our results is difficult. More recently, Sonesson et al. reported an overall incidence of 34% and a prevalence of 78% at five years (K&L grade ≥2).[31] Sixty percent of participants treated with APM compared to 37% in the non-surgery group progressed radiographically (K&L ≥1 grade increase). However, these results must be interpreted with caution, as only as-treated analyses were conducted, and the retention rate was low. Finally, two separate analyses of the MeTeOR trial evaluated progression of MRI-based OA markers over 18 months and the incidence of total knee replacement at five years.[30,244] The APM group showed greater advancement of MRI-based OA markers over 18 months compared to the exercise group, including osteophyte size and cartilage surface area.[244] At five years, a greater likelihood of total knee replacement was observed for participants randomized to APM compared to those randomized to exercise (hazard ratio 2.0, 95% CI 0.8 to 4.9).[30] In addition to differences in the study population (70% with radiographic knee OA at baseline), an important distinction to the OMEX trial is the use of MRI to detect OA changes at 18 months. While no evidence of between-group differences was found for individual OA features evaluated by radiography

at five years in the OMEX trial, one cannot rule out that the use of sensitive MRI sequences would yield different results.

In the placebo-controlled FIDELITY trial, 72% in the APM group and 60% in the placebo group progressed at least one K&L grade over five years.[33] Furthermore, the OARSI sum score indicated more progression in the APM group. The authors conclude that APM was associated with increased risk of OA progression. Yet, the clinical relevance has been questioned as the between-group differences were small for both K&L (risk difference 13%, 95% CI -2% to 28%) and OARSI sum score (mean difference 0.7, 95% CI 0.1 to 1.3).[245] Nevertheless, the result for the OARSI sum score is in slight contrast to the OMEX trial (mean difference -0.02, 95% CI -0.53 to 0.49). One possible explanation is their cross-over rate of 11%, compared to 20% in the OMEX trial. Another distinction is the presence of radiographic OA changes at baseline. Twenty-nine percent of the FIDELITY trial participants had no radiographic knee OA changes (K&L grade 0), 53% had some radiographic OA change (K&L grade 1), and 18% had radiographic knee OA (K&L grade 2).[33] In comparison, 69% of the OMEX trial participants had no radiographic knee OA changes, and only 3% had radiographic knee OA. Structural progression likely accelerates at more advanced stages of the disease, and the OMEX trial participants may not have reached the point of rapid progression at the five-year follow-up.

Consistent with the five-year results in the other randomized trials,[22,30,31,33] no statistically significant or clinically relevant between-group differences were observed for patient-reported outcomes. For both treatment groups, the absolute KOOS subscale scores at five years were close to or above 90 points for pain, symptoms, and ADL. For KOOS sport/rec and QoL, the scores were between 74 and 79 points, which is approximately 10 points worse than age-specific reference data.[165] This indicates that both treatment groups, on average, showed clinically relevant improvements and had considerably less knee function impairments compared to baseline when KOOS sport/rec and QoL subscale scores were more than 40 points worse than reference data. However, 10 points worse score compared to reference data at five years also indicates that degenerative knee changes and not only meniscal damage per se cause knee impairments.

Paper II

Heterogeneity of treatment response is not accounted for in randomized controlled trials, and the average effect may not be applicable to individual patients.[52] The identification of three distinct trajectories of patient-reported pain and knee function shed new light on impairments and longitudinal improvements in patients treated for degenerative meniscal tears.

In line with our findings of a *low, minimal improvement* trajectory (10%-12% of the participants), a subgroup of approximately 10% with severe impairments and minimal improvement has been consistently identified in numerous trajectory studies in the knee OA population.[144,146,147,246-248] However, for the other trajectories identified, there are apparent differences between the degenerative meniscal tear population and the more severe knee OA population. More than 87% of our middle-aged degenerative meniscal tear patients without radiographic knee OA were identified in a *moderate, gradual improvement* (20%-36%) or *high*, *early improvement trajectory* (53%-70%). In the older and more severe knee OA population, none[147,247] or only a minority,[146,246,248] have been identified in trajectories characterized by marked improvement over time. The strong potential for improvement is important information for clinicians and should be included in patient education programs for individuals presenting with a symptomatic degenerative meniscal tear.

Previous studies have tried to demonstrate the existence of subgroups following treatment with APM or exercise therapy based on baseline variables, but statistical multivariable prognostic models and surgeons' predictions failed to predict treatment outcome accurately.[140,143,249] We identified a range of baseline factors as prognostic for function in sport and recreation, several of which have not been considered in the aforementioned studies. However, future studies are necessary to confirm the ability to identify patients with poor prognosis based on these factors and the effect of addressing them to improve long-term outcomes.

Consistent with findings in the knee OA population,[144,146,250] greater knee pain, higher BMI, poorer mental health, and higher K&L grade at baseline was associated with being in a trajectory characterized by more severe knee function impairments and minimal improvement over time. Furthermore, trajectories characterized by low KOOS sport/rec function were also associated with more meniscal extrusion and lower subjective knee function. Clinicians should therefore consider these factors to identify patients with poor prognosis. Potentially modifiable prognostic factors are of particular interest as these may be

treatment targets to improve long-term outcomes. In addition to higher BMI and lower psychological health, lower knee muscle strength and worse functional performance were modifiable prognostic factors for the low KOOS sport/rec trajectory. Finally, physical activity level may also influence prognosis; only one in every five participants in the low KOOS sport/rec trajectory compared to one in every two participants in the high trajectory performed physical activity ≥150 minutes per week before their knee complaints.

It is noteworthy that the fundamental components (exercise, lifestyle physical activity, and weight management) in current OA management programs [251] address the prognostic factors identified for the degenerative meniscal tear population without radiographic knee OA. Furthermore, these programs emphasize patient involvement and education, which may facilitate adherence to interventions targeting prognostic factors.[252] Given the robust evidence supporting the beneficial effect on pain, function, and risk for OA development,[48,106,253-256] these treatment modalities should be considered for degenerative meniscal tear patients presenting with severe impairments.

Paper III

Muscle strength deficits compared to the contralateral leg of 11% to 14% for normalized quadriceps strength and 1% to 7% for normalized hamstrings strength were seen at baseline for the two treatment groups. Lower limb disuse due to pain and symptoms as well as arthrogenic muscle inhibition are likely contributors to the strength reductions.[119,257] The magnitude of strength deficits at baseline is consistent with findings in a previous investigation.[258]

Exercise therapy was effective in improving knee muscle strength up to 12 months compared to APM. Improvements of 11% to 18% were seen for normalized quadriceps and hamstrings strength at three months for the exercise group, and absolute muscle strength was similar (quadriceps) or higher (hamstrings) compared to the non-involved leg at baseline. Thus, twelve weeks of twice-weekly exercise therapy seems to be sufficient to attenuate knee muscle strength deficits in individuals with degenerative meniscal tears. The improvements were further maintained up to 12 months. In contrast, APM was associated with a slight decline (-4% to -2%) in normalized quadriceps strength at three months and only minor improvements at 12 months (4% to 6%). Overall, this suggests that at least 12 months is necessary to regain normal quadriceps strength following surgery. Similar courses of knee

muscle strength at three and 12 months following surgery have been previously reported in a small cohort study including degenerative meniscal tear patients with no or minimal OA (K&L grade 0-1).[258] Although there is little knowledge regarding the consequences of periods of knee muscle weakness, early restoration of quadriceps strength may be important to reduce the risk for knee OA development.

At follow-up after five years, between-group differences were attenuated. Only a small statistically significant between-group difference in favor of the exercise group remained for hamstrings strength. No previous studies have compared longitudinal muscle strength changes up to five years following exercise therapy or APM for degenerative meniscal tears. However, quadriceps muscle strength four years after APM has been compared to healthy controls in three observational studies[259-261] and more recently summarized in a meta-analysis.[118] Moderate reductions in quadriceps strength were seen four years after APM, which equates to an approximately 11% to 12% difference compared to healthy controls.[118] In our two treatment groups, reductions in strength were seen from 12 months to five years, which may reflect progression to more severe knee OA changes or disease onset. However, similar reductions in the contralateral leg indicate that for these individuals, with the majority entering their fifth or sixth decade of life, the decline is likely age-related.[262]

Quadriceps muscle weakness at baseline was further identified as a risk factor for progression to more severe OA changes. For every 0.2 N·m/kg decrease in quadriceps muscle strength the odds of radiographic progression increased by 40%. Although most participants with radiographic progression only increased their K&L grade from 0 to 1 (44 out of 65 participants, 68%), this change is of clinical relevance as grade 1 is an important indicator of longitudinal incident disease.[206,263] In a previous observational study, the presence of a doubtful osteophyte (K&L grade 1) was associated with a 4.5-fold increased risk of developing radiographic knee OA (K&L grade ≥2) over 15 years compared to knees graded as K&L 0.[206] Quadriceps muscle weakness has been found to be a risk factor for incident radiographic knee OA in the general population,[47] although conflicting evidence exists.[264] For individuals with degenerative meniscal tears specifically, a small study found quadriceps and hamstrings muscle weakness four years after APM to be associated with more severe OA changes 11 years later.[49] This is consistent with the increased risk associated with quadriceps weakness at baseline in our study. Thus, early interventions addressing quadriceps muscle weakness seems important to attenuate the risk for progression to more severe OA changes

for the degenerative meniscal tear population. The results from a longitudinal cohort study also partly support this, as quadriceps weakness was associated with incident knee OA over seven years in women but not in men with degenerative meniscal tears not receiving any treatment.[48]

Conclusions

The present thesis investigated the long-term consequences of APM compared to exercise therapy for symptomatic degenerative meniscal tears. This five-year follow-up study adds to the growing evidence of treatment effects for degenerative meniscal tears and provides novel knowledge specifically for the middle-aged population with no or minimal concomitant radiographic knee OA. The conclusions based upon the results from the three papers are:

I. Five years following APM or exercise therapy for degenerative meniscal tears, there was no evidence for between-group differences in progression of radiographic OA changes or development of knee OA.

II. For both APM and exercise therapy, improvements in patient-reported pain and knee function were clinically relevant, but neither treatment was superior at five years.

III. Three distinct trajectories of patient-reported pain and knee function have been identified in individuals with degenerative meniscal tears. Nine in every 10 individuals improve early or gradually over two years, whereas one in 10 experience severe pain and functional limitations with minimal improvement over five years. To improve long-term knee function, prognostic factors such as BMI, mental health, knee muscle strength, and functional performance may be appropriate treatment targets.

IV. Twelve weeks of exercise therapy effectively improved quadriceps and hamstrings muscle strength up to 12 months compared to APM. Between-group differences in knee muscle strength were attenuated at follow-up after five years.

V. Quadriceps muscle weakness at baseline was a risk factors for radiographic knee OA progression over five years.

Implications

- Exercise therapy should be the first-line treatment for symptomatic degenerative meniscal tears, and continued efforts are needed to reduce surgery rates further. Patients presenting to clinical practice should be informed that APM provides no additional benefit in radiographic or clinical outcomes.

- A small subgroup of degenerative meniscal tear patients experiences severe pain and reduced knee function over time and needs to be identified early to improve long-term outcomes. Multimodal treatment programs focusing on patient-education, exercise, lifestyle physical activity, and weight management when indicated, may be future steps to improve patient care for this early knee OA population.

- Quadriceps muscle weakness may play a role in progression of radiographic knee OA changes, and early interventions targeting knee muscle strength should be recommended for degenerative meniscal tear patients. Improvements in knee muscle strength following a 12-week exercise therapy program further support the ongoing shift in treatment strategy for degenerative meniscal tears, recommending exercise therapy over surgery.

Future perspectives

Studies with longer follow-up periods than five years are needed to improve the knowledge of long-term consequences of degenerative meniscal tears. Currently, the clinical meaning of the observed radiographic changes is unknown. Continued research is warranted to bridge this research gap: do early radiographic changes predict future pain, knee function impairments, and risk of total knee replacement.

Future research aimed at identifying subgroups with differential treatment responses is also needed to steer us towards a more individualized approach. Individual patient data meta-analysis may allow for more accurate identification of subgroups not responding to treatment and has recently been initiated.[265] Such efforts and new high-quality studies may also provide further insights into specific patient characteristics linked to OA disease mechanisms. Knee OA constitutes an enormous individual and societal burden, and the ultimate goal of future research must be to reduce the risk of OA development and progression.

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III

Original article

Running Head: Muscle strength following treatment for degenerative meniscal tears

Full Title: Muscle strength and osteoarthritis progression after surgery or exercise for degenerative meniscal tears: Secondary analyses of a randomized trial

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Conflicts of interest: Bjørnar Berg report grant from the South-Eastern Norway Regional Health Authority. Ewa Roos is the Deputy editor of Osteoarthritis and Cartilage, the developer of Knee injury and Osteoarthritis Outcome Score and several other freely available patient-reported outcome measures, and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D), a non-for profit initiative to implement clinical guidelines in primary care. Nina Jullum Kise declare no conflict of interest. Lars Engebretsen declare no conflict of interest. Inger Holm is co-founder of Active Living with Osteoarthritis (AktivA), a non-for profit initiative to implement clinical guidelines of knee and hip OA in primary care. May Arna Risberg report grant from the South-Eastern Norway Regional Health Authority, is Guest editor for Special Issue 2021 Osteoarthritis and Cartilage, and co-founder of Active Living with Osteoarthritis (AktivA), a non-for profit initiative to implement clinical guidelines of knee and hip OA in primary care

ABSTRACT

Objective: To evaluate muscle strength changes following partial meniscectomy or exercise therapy for degenerative meniscal tears and the relationship between baseline muscle strength and osteoarthritis progression.

Methods: Secondary analysis of a randomized trial (n=140 participants). Isokinetic quadriceps and hamstrings strength (peak torque [N·m/kg] and total work [J/kg]) were assessed at baseline, three-, 12-month, and five-year follow-up. Between-group differences were analyzed using intention-to-treat linear mixed models. The relationship between baseline muscle strength and osteoarthritis progression (Kellgren and Lawrence, ≥1 grade increase) were assessed using logistic regression models.

Results: We found statistically significant between-group differences favoring exercise therapy at three months (quadriceps: -0.30 N·m/kg, 95% CI -0.40, -0.20; hamstrings: -0.10 N·m/kg, 95% CI -0.15, -0.04) and 12 months (quadriceps: -0.13 N·m/kg, 95% CI -0.23, -0.03; hamstrings: -0.08 N·m/kg, 95% CI -0.14, -0.03). At five years, between-group differences were -0.10 N·m/kg (95% CI -0.21 to 0.01) for quadriceps and -0.07 N·m/kg (95% CI -0.13 to -0.01) for hamstrings. Quadriceps muscle weakness at baseline was associated with knee osteoarthritis progression over five years: adjusted odds ratio of 1.40 for every 0.2 N·m/kg decrease (95% CI 1.15 to 1.71). The adjusted odds ratio for hamstrings was 1.14 (95% CI 0.97-1.35) for every 0.1 N·m/kg decrease.

Conclusion: Exercise therapy was effective in improving muscle strength at three and 12-month follow-up compared to partial meniscectomy, but the effect was attenuated at five years. Quadriceps muscle weakness at baseline was associated with higher odds of osteoarthritis progression over five years.

Significance and Innovations

- Twelve weeks of exercise therapy is effective in improving knee muscle strength up to 12 months compared to partial meniscectomy in middle-aged individuals with degenerative meniscal tears
- Quadriceps muscle weakness at baseline is a risk factor for radiographic knee osteoarthritis progression over five years
- Our results highlight that early interventions targeting knee muscle strength should be recommended for degenerative meniscal tear patients and support the ongoing shift in treatment strategy for this patient population, recommending exercise therapy over surgery

Knee muscle weakness is a typical feature of patients with symptomatic degenerative meniscal tears (1, 2). Lower limb disuse and atherogenic muscle inhibition are possible contributing factors (3, 4). Following arthroscopic partial meniscectomy, surgery-induced trauma and post-surgery disuse may further augment muscular dysfunctions and prolong muscle weaknesses (1, 3). A 2015 meta-analysis showed that partial meniscectomy patients had a moderate reduction in knee extensor muscle strength before surgery, at six months, and four years post-surgery (1).

Muscle strengthening is suggested as one of the mechanisms underlying the beneficial effect of exercise therapy in knee osteoarthritis, with studies reporting a direct longitudinal association between increased knee muscle strength and reductions in activity limitations and pain (5, 6). For degenerative meniscal tear patients, a 12-week exercise therapy program consisting of progressive neuromuscular and strengthening exercises significantly improved knee muscle strength (7). However, the course of knee muscle strength changes during the five years following arthroscopic partial meniscectomy or exercise therapy as treatments for degenerative meniscal tears remains unknown.

Knee muscle weakness may be an independent risk factor for radiographic knee osteoarthritis development or progression to more severe osteoarthritis changes in the general (8, 9) and degenerative meniscus population (10, 11). Identifying and targeting single pathways to osteoarthritis in early disease stages is likely more effective than when the disease has progressed and become more complex (12). Degenerative meniscal tears are part of the osteoarthritic process and a precursor to radiographic knee osteoarthritis (13). Subsequent radiographic changes, such as osteophyte formation and joint space narrowing, represents more significant joint damage. These radiographic features' presence and progression are potentially clinically relevant, both for increased pain and risk of incident disease (14, 15). Ascertaining muscle

strength as a potential risk factor has at least two important clinical implications: (i) facilitate the shift toward a proactive treatment approach which allow for a greater chance to prevent or slow osteoarthritis progression (12, 16), and (ii) support the ongoing shift in treatment strategy for degenerative meniscal tears recommending exercise therapy over surgical treatment (17).

In the Odense-Oslo Meniscectomy versus Exercise (OMEX) trial, arthroscopic partial meniscectomy was compared to exercise therapy for degenerative meniscal tears. Between-group differences in knee muscle strength changes have been previously reported at three- and 12-month follow-up (18). However, no longitudinal analysis, including muscle strength assessment at five years, has been performed. Furthermore, the influence of muscle strength on osteoarthritis progression has not earlier been ascertained in our trial. We also extend existing knowledge by reporting body weight normalized muscle strength, within-group changes and absolute knee muscle strength for the involved and uninvolved leg, and proportions of patients with clinically relevant improvements in the two treatment groups.

Accordingly, the aim of this five-year follow-up study of the randomized controlled OMEX trial was to evaluate normalized knee muscle strength and longitudinal changes following arthroscopic partial meniscectomy and exercise therapy as treatments for degenerative meniscal tears. We also examined the association between baseline knee muscle strength and osteoarthritis progression over five years.

PATIENTS AND METHODS

Study design and participants

We conducted a randomized controlled trial involving participants aged 35-60 years with non-

traumatic unilateral knee pain (>2 months), recruited from two orthopedic departments in Norway (October 2009-September 2012). All participants had a degenerative medial meniscal tear verified by magnetic resonance imaging (MRI), Kellgren and Lawrence grade ≤2, and were considered eligible for surgery by one of two orthopedic surgeons based on patient history, physical examination, and MRI findings.

The sample size was calculated based on detecting a 10-point difference with a standard deviation of 15 in the change in $KOOS_4$ at the primary endpoint (two-year follow-up) (18). Accounting for an estimated dropout-rate of 15% and 20% crossover rate, 140 participants were randomized (1:1 ratio). No a priori power calculations were performed for this five-year follow-up study. An independent statistician determined the computer-generated randomization sequence, stratified by sex in blocs of eight, and concealed the allocations in sequentially numbered opaque envelopes. The test assessors were blinded to group allocation at baseline, three, and 12 months. To preserve blinding, the participants wore long pants or neoprene sleeves.

The trial was registered at ClinicalTrials.gov (NCT01002794) and conducted according to the Declaration of Helsinki. The ethics committee of the Health Region of South-East Norway approved the trial (ref-no 2009/230). All participants gave written informed consent.

Deviations from trial registration

In the trial registration (NCT01002794), muscle strength tests were registered at three and 24 months. Due to financial and logistic constraints, isokinetic muscle strength tests were conducted at 12 months instead of 24 months. Additionally, we included muscle strength tests at the five-year follow-up since muscle weakness has been shown to persist up to four years after partial meniscectomy (1).

Interventions

The 12-week exercise therapy program consisted of progressive neuromuscular and strengthening exercises. Experienced physical therapists at the Norwegian Sports Medicine Clinic (NIMI) or Gnist Trening og Helse AS followed a standardized protocol (19). The participants performed two to three sessions per week, and physical therapists supervised one of the weekly sessions.

Experienced surgeons performed the arthroscopic partial meniscectomy using anteromedial and anterolateral portals. A diagnostic procedure, including systematic probing of both menisci, was followed by resection of all unstable meniscal tissue. Pre- or post-operative physical therapy was not part of the intervention, but the participants were given instructions for simple home exercises to regain range of motion and reduce swelling. Both interventions have been previously described in detail (18, 19).

Outcomes

Isokinetic muscle strength testing

Quadriceps and hamstrings muscle strength was assessed using an isokinetic dynamometer (Biodex 6000, Shirley, New York, USA) at baseline, three and 12 months, and five years. Both legs were tested, and the testing order was determined by randomization. The same order was applied at all follow-ups. Trained assessors followed a detailed protocol to test concentric knee extension and flexion at 60°/seconds in the range from 90° flexion to full extension. Visual inspection and manual palpation were used to align the anatomical axis of rotation to the dynamometer axis. Baseline chair settings were recorded to duplicate the testing position at the

subsequent follow-ups. Following a 10-minute warm-up on a stationary bike, the participants were placed in an upright seated position with shoulder and abdominal straps to minimize body movements. The participants performed four trial repetitions, followed by 1-minute rest and five maximal test repetitions. We used body weight normalized peak torque (Newton meters [N·m]: N·m/kg) and total work (Joules [J]: J/kg) in the data analyses. Peak torque represents the highest muscular force output at any moment during the test bout, and total work represents the amount of work accomplished during the five maximal repetitions (20). The reliability of isokinetic knee muscle testing is high (21-23). Based on the results from the test-retest studies, we defined participants as responders for normalized quadriceps and hamstrings strength at each follow-up if a change from baseline of at least 15% for quadriceps and at least 20% for hamstrings was detected. A change of 15% for quadriceps strength has previously been used as a clinically important cutoff for knee osteoarthritis patients (24).

Knee osteoarthritis progression

Radiographs were acquired at baseline (recruiting hospitals) and five years (private radiology clinic) using a standardized protocol (25). The protocol included posterior-anterior radiographs, 10° caudal X-ray beam angulation, and the use of a Synaflexer (Synarc, Newark, CA) positioning frame (26). Two experienced radiographic readers, blinded to clinical data, graded all radiographs according to the Kellgren and Lawrence classification (0-4, normal to severe) (27). The radiographs were re-read in cases of between-reader discrepancy and discussed until consensus was reached. Inter-rater reliability for the two readers has been previously evaluated for the Kellgren and Lawrence classification (weighted k 0.67) (28). We defined osteoarthritis progression as increase of ≥1 grade from baseline to five years (dichotomous outcome: Yes or No). Participants undergoing an osteotomy or total knee replacement were also considered to

have progressed radiographically.

Patient involvement

There was no patient involvement in the planning or conduct of the study, but user involvement was included in implementation of the exercise therapy program. User experiences and results from the OMEX trial are disseminated to clinicians and patients through AktivA, a nationally implemented osteoarthritis treatment program (29).

Statistical analyses

The primary analyses of knee muscle strength changes were performed on an intention-to-treat basis. We used linear mixed models to analyze between-group differences in change from baseline to each follow-up. The outcomes were normalized quadriceps and hamstrings muscle strength (peak torque and total work) at three and twelve months and five years. The models were adjusted for sex (randomization stratification variable) and baseline value of the outcome. Participants were included as random effect with random intercept and slopes, and time-point (baseline, three and 12 months, and five years), time × treatment interaction, and sex as fixed effects. One outcome variable (hamstrings total work) was modeled with random intercept due to convergence difficulties. To adjust for baseline differences, we did not include a main effect for treatment group in the model (30). From the fitted models, we present estimated mean change values and 95% confidence intervals (95% CI) at each follow-up for both treatment groups and between-group differences in change from baseline. We also report absolute knee muscle strength in the involved and uninvolved leg at each time-point for the two treatment groups.

Proportions in the two treatment groups with improvements above 15% for quadriceps and above 20% for hamstrings (responders) were compared at each follow-up using the chi-square test. For these analyses, participants with incomplete outcome data were excluded from the actual time-point with missing data.

For our secondary aim, normalized quadriceps and hamstrings muscle strength (N·m/kg) at baseline were the exposures and osteoarthritis progression (Kellgren and Lawrence, increase of ≥1 grade) over five years was the outcome. A complete-case analysis was applied, excluding participants with missing outcome data at the five-year follow-up (n=20). We pooled data from both treatment groups because preliminary analyses showed no significant treatment × quadriceps interaction (Odds ratio [OR] 1.17, 95% CI 0.85 to 1.61) or treatment × hamstrings interaction (OR 1.29, 95% CI 0.96 to 1.72). Separate logistic regression analyses were conducted for quadriceps and hamstrings peak torque to avoid multicollinearity. Models were adjusted for gender, baseline Kellgren and Lawrence grade, and the baseline pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (31). Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. Continuous variables were linearly related to the logit of the dependent variable (assessed using the Box-Tidwell approach). There were no standardized residuals with a value of ±2 standard deviations.

Analyses were performed using Stata V.16.1 (StataCorp, College Station, TX, US).

RESULTS

All 140 participants were included in the primary analyses (Figure 1**)**. In the exercise group, ten participants declined exercise therapy. Four of these participants, and ten participants who participated in the exercise therapy program, crossed over to receive partial meniscectomy. Six

participants in the partial meniscectomy group did not undergo surgery. One participant who crossed over from the exercise group and one participant in the partial meniscectomy group received a high tibial osteotomy four to six months after the index partial meniscectomy. Three participants in the partial meniscectomy group underwent another partial meniscectomy 12, 15, and 36 months after the index partial meniscectomy. One participant in the partial meniscectomy group received a total knee replacement 34 months after the index partial meniscectomy. Table 1 gives patient characteristics at baseline for the participants in the two treatment groups.

Knee muscle strength change

Table 2 presents estimated change in normalized quadriceps and hamstrings strength at three and 12 months and five years. Changes in normalized quadriceps and hamstrings peak torque are also illustrated in Figure 2. At three months, we found statistically significant between-group differences for change in normalized quadriceps (-0.30 N·m/kg, 95% CI -0.40 to -0.20) and hamstrings peak torque (-0.10 N·m/kg, 95% CI -0.15 to -0.04) favoring the exercise group (Table 2). Forty-four percent of the exercise group participants were classified as responders for normalized quadriceps peak torque (≥15% change from baseline) compared to 16% in the partial meniscectomy group (p=<0.001 for between-group difference). The proportion of responders for normalized hamstrings peak torque (≥20% change from baseline) were 35% in the exercise group and 18% in the partial meniscectomy group (p=0.033) (Supplementary Table 1).

At 12 months, the exercise group had maintained the improvements achieved at three months. Between-group differences at 12 months were statistically significant in favor of the exercise group for changes in normalized quadriceps (-0.13 N·m/kg, 95% CI -0.23 to -0.03) and hamstrings peak torque (-0.08 N·m/kg, 95% CI -0.14 to -0.03) (Table 2). In the exercise group,

42% and 34% of the participants were responders for normalized quadriceps and hamstrings peak torque, respectively. The corresponding numbers for the partial meniscectomy group were 26% and 19% (p-value for between-group difference: 0.054 [quadriceps] and 0.070 [hamstrings]) (Supplementary Table 1).

At five years, we found a statistically significant between-group difference for change in normalized hamstrings peak torque in favor of the exercise group, but the difference was small (-0.07 N·m/kg, 95% CI -0.13 to -0.01). We found no statistically significant between-group difference for normalized quadriceps peak torque (-0.10 N·m/kg, 95% CI -0.21 to 0.01) (Table 2**)**. Muscle strength declined in both groups from 12 months to five years. However, normalized quadriceps strength at five years was higher compared to baseline in the exercise group (0.13 N·m/kg, 95% CI 0.05 to 0.20) and equal in the partial meniscectomy group (0.03 N·m/kg, 95% CI -0.05 to 0.10). For normalized hamstrings strength, differences were small compared to baseline; a slight improvement in the exercise group (0.04 N·m/kg, 95% CI 0.00 to 0.09) and no difference for the partial meniscectomy group (N·m/kg -0.02, 95% CI -0.07 to 0.02). Twenty-eight percent in the exercise group and 20% in the partial meniscectomy group were responders for normalized quadriceps peak torque (p=0.331). The proportion of responders for normalized hamstrings peak torque was 23% (exercise group) and 10% (partial meniscectomy group) (p=0.066) (Supplementary Table 1). Absolute knee muscle strength for the involved and uninvolved leg at all follow-ups is displayed in Supplementary Table 2.

Association between baseline knee muscle strength and radiographic progression

Sixty-five of 120 participants (54%) were defined as having progressed radiographically: 31 in the exercise group (54%) and 34 in the partial meniscectomy group (55%). Overall, the

proportion of women was higher in the progression (43% women) compared to the non-progression group (33% women). Participants with progression also had slightly higher BMI and more knee pain at baseline (Supplementary Table 3). We found that quadriceps muscle weakness at baseline was significantly associated with increased odds of radiographic progression. In the crude model adjusted only for gender, the odds of radiographic progression increased by 33% for every 0.2 N·m/kg decrease in quadriceps strength (OR 1.33, 95% CI 1.13 to 1.58). In the model adjusted for gender, knee pain and Kellgren and Lawrence grade at baseline, the odds increased by 40% for every 0.2 N·m/kg decrease in quadriceps strength (OR 1.40, 95% CI 1.15 to 1.71). The crude and adjusted odds ratios for every 0.1 N·m/kg decrease in hamstrings strength were 1.14 (95% CI 0.99 to 1.32) and 1.14 (95% CI 0.97 to 1.35), respectively (Table 3). The goodness-of-fit test for crude and adjusted models for quadriceps and hamstrings showed that the models were adequate (P>0.05).

DISCUSSION

Twelve weeks of twice-weekly exercise therapy effectively improved quadriceps and hamstrings muscle strength in degenerative meniscal tear patients compared to arthroscopic partial meniscectomy alone up to 12 months. While participants in the exercise group still had greater quadriceps strength at five years compared to baseline, there was no longer any statistically significant between-treatment group difference. We also found that for middle-aged individuals with degenerative meniscal tears and without radiographic osteoarthritis, lower quadriceps strength at baseline increased the odds of radiographic osteoarthritis progression over five years by 40% (for every 0.2 N·m/kg decrease).

Consistent with a previous investigation (2), muscle strength at baseline in the two treatment groups was 11%-14% lower for quadriceps compared to the contralateral leg and 1%-7% lower for hamstrings. Interestingly, muscle strength in the involved leg at baseline (Table 1) was equivalent to normative age-matched data for quadriceps peak torque (1.98 N·m/kg), but lower for hamstrings peak torque (1.17 N·m/kg) (32).

At three months, we found between-group differences of 15% for change in normalized quadriceps peak torque and 10% for normalized hamstrings peak torque. Following a slight decline in normalized quadriceps strength at three months, improvements were also seen for the partial meniscectomy group at 12 months, but between-group differences were still statistically significant. A previous investigation found no bilateral differences in quadriceps strength 12 months post-operatively (2). However, our partial meniscectomy group's affected leg was 6% weaker than the uninvolved leg at 12 months, and only one in four participants were defined as responders (cutoff of 15% change).

Muscle strength declined from 12 months to five years in both treatment groups. This is expected as the mean age at inclusion was 50 years; the threshold when age-related declines in strength generally commence (33). We also saw a similar decline in the uninvolved leg, which corroborates the decline as age-related. Still, five-year absolute muscle strength was 4%-6% higher than baseline for the exercise group and between 1% higher to 3% lower for the partial meniscectomy group. Although this may partly be explained by disuse before study inclusion, our OMEX trial included highly physically active individuals: approximately eight in 10 participated in sport or exercise activities ≥150 minutes/week before their knee problems (34). Moderate to vigorous physical activity is beneficially associated with lower limb muscle strength (35). In a previous study also including individuals reporting high physical activity level before

diagnosis, no difference in muscle strength compared to healthy controls was found two years after partial meniscectomy or in changes from two to four years (36, 37). In contrast, in persons not participating in any sporting activities, 24% lower quadriceps strength than matched controls have been found four years post-surgery (38). This may indicate that in physically inactive persons with potentially less spare muscle capacity at diagnosis, surgery and the extended period of inactivity could have more detrimental effects on muscle strength that are difficult to restore without a structured intervention program focusing on knee muscle strength.

Knee muscle weakness alters the mechanical environment and may affect cartilage integrity negatively (39). Our results support this and indicate that quadriceps muscle strength is important for the risk of progression to more severe osteoarthritis changes in middle-aged individuals with degenerative meniscal tears. A recent small study found that lower knee muscle strength four years after partial meniscectomy was associated with more severe osteoarthritis changes 11 years later (11). Our larger study complements these findings by identifying baseline muscle weakness as a risk factor for progression to more severe osteoarthritis changes five years later. Identification of a modifiable pathway to osteoarthritis in this patient population known to already be at increased risk for disease development indicates that early interventions addressing knee muscle strength should be recommended for all degenerative meniscus individuals.

The mean difference in normalized quadriceps peak torque at baseline between participants with and without radiographic progression was almost 0.4 N·m/kg. For men and women, respectively, the deficit was 15% and 22% compared to those without progression. The adjusted odds ratio for every 0.2 N·m/kg decrease was 1.40 (95% CI 1.15 to 1.71); the odds of radiographic progression increased by 40%. While we in the current study found improvements in quadriceps strength following 12 weeks of exercise therapy of more than 0.2 N·m/kg, participants with radiographic

progression over five years were well balanced concerning treatment received (48% from the exercise group). Thus, it is likely that participants in the exercise group with osteoarthritis progression did not achieve adequate quadriceps strength following the intervention to fully eliminate quadriceps muscle weakness as a risk factor for progression. For instance, progressors in the exercise group had a mean deficit of approximately 10% at three months compared to the uninvolved leg. In comparison, non-progressors had equal quadriceps strength in the affected and uninvolved leg at the same time-point. To achieve positive effects on muscle strength, compliance to exercise is essential. Clinicians are important facilitators to promote compliance through individually tailored exercises, patient education, and patient involvement (40).

The present study has limitations. No power calculations were performed a priori for this five-year follow-up study. However, for between-group differences in knee muscle strength changes, the confidence intervals of the effect estimates indicate appropriate statistical power. We evaluated peak torque and total work, but other parameters such as angle-specific torque may provide additional information in degenerative meniscus individuals (41). Six participants in each group did not receive any treatment, and 14 (20%) crossed over from exercise to partial meniscectomy. However, we believe this reflects clinical practice. We included middle-aged physically active individuals, and the results are not generalizable to older, less physically active individuals with concomitant osteoarthritis. Finally, the sample size prevented us from stratifying osteoarthritis progression analyses by sex.

In conclusion, 12 weeks of exercise therapy was effective in improving quadriceps and hamstrings muscle strength compared to arthroscopic partial meniscectomy for middle-aged patients with degenerative meniscal tears. We found statistically significant differences in change from baseline to three and 12 months in favor of the exercise group. At five years, between-

group differences were attenuated and no longer statistically significant for quadriceps strength. We also found evidence to suggest that lower quadriceps strength at baseline is associated with radiographic knee osteoarthritis progression over five years.

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Table 1. Baseline characteristics of participants randomized to exercise therapy (ET) or arthroscopic partial meniscectomy (APM)

Characteristics	**ET group (n=70)**	**APM group (n=70)**
Sex, men	43 (61)	43 (61)
Age (years)	50.2 ± 6.4	48.9 ± 6.3
Body mass index (kg/m^2)	26.5 ± 4.3	26.0 ± 3.7
Pain duration (months)[1]	9.5 (13.6)	6.0 (7.0)[2]
Kellgren & Lawrence:		
Grade 0	49 (70.0)	48 (68.6)
Grade 1	20 (28.6)	19 (27.1)
Grade 2	1 (1.4)	3 (4.3)
Quadriceps peak torque (N·m/kg)		
Involved leg	1.95 ± 0.57	2.03 ± 0.59
Uninvolved leg	2.22 ± 0.51	2.27 ± 0.51
Quadriceps total work (J/kg)		
Involved leg	9.57 ± 2.83	9.85 ± 2.91
Uninvolved leg	10.63 ± 2.44	10.89 ± 2.40
Hamstrings peak torque (N·m/kg)		
Involved leg	1.02 ± 0.32	1.10 ± 0.29
Uninvolved leg	1.07 ± 0.28	1.11 ± 0.28
Hamstrings total work (J/kg)		
Involved leg	5.50 ± 2.06	6.15 ± 1.9
Uninvolved leg	5.84 ± 1.81	6.22 ± 1.67

Values are numbers (percentages) or means ± standard deviations unless otherwise stated

N·m/kg=Newton meter/kilograms; J/kg=Joule/kilograms

[1]Median (interquartile range)

[2]Missing data from one participant

Table 2. Estimated change from baseline to follow-ups and between-group differences in knee muscle strength for the exercise therapy (ET) and arthroscopic partial meniscectomy group (APM)

	3 months			**12 months**			**5 years**		
	Difference*			**Difference***			**Difference***		
	ET (n=63)	APM (n=61)	Δ	ET (n=59)	APM (n=62)	Δ	ET (n=57)	APM (n=59)	Δ
Quadriceps									
Peak torque	0.26	-0.04	-0.30	0.24	0.12	-0.13	0.13	0.03	-0.10
95% CI	0.19, 0.34	-0.11, 0.04	-0.40, -0.20	0.17, 0.32	0.04, 0.19	-0.23, -0.03	0.05, 0.20	-0.05, 0.10	-0.21, 0.01
Total work	1.04[1]	-0.35	-1.39	1.11	0.36	-0.74	0.48	0.15	-0.34
95% CI	0.68, 1.40	-0.70, 0.01	-1.89, -0.88	0.74, 1.47	0.01, 0.72	-1.25, -0.24	0.11, 0.86	-0.22, 0.51	-0.86, 0.18
Hamstrings									
Peak torque	0.16	0.06	-0.10	0.14	0.06	-0.08	0.04	-0.02	-0.07
95% CI	0.12, 0.20	0.02, 0.11	-0.15, -0.04)	0.10, 0.19	0.02, 0.10	-0.14, -0.03	0.00, 0.09	-0.07, 0.02	-0.13, -0.01
Total work	1.00[1]	0.30	-0.70	0.86	0.33	-0.54	0.30	-0.20	0.50
95% CI	0.73, 1.27	0.03, 0.57	-1.08, -0.32)	0.59, 1.14	0.06, 0.60	-0.92, -0.15	0.02, 0.58	-0.47, 0.08	-0.89, -0.11

Values are mean (95% confidence interval)

*APM group is reference group

Δ Between-group difference in change

Peak torque=Newton meter/kilograms; Total work=Joule/kilograms

[1]n=62

Table 3. Association between baseline knee muscle strength (N·m/kg) and radiographic knee osteoarthritis progression over five years

	Knee osteoarthritis progression		
	Progressors (n=65)	Non-progressors (n=55)	*P*-value
Quadriceps strength (0.2 Nm/kg decrease)			
Crude odds ratio (95% CI)[a]	1.33 (1.13-1.58)	1.0 (reference)	0.001
Adjusted odds ratio (95% CI)[b]	1.40 (1.15-1.71)	1.0 (reference)	0.001
Hamstrings strength (0.1 Nm/kg decrease)			
Crude odds ratio (95% CI)[a]	1.14 (0.99-1.32)	1.0 (reference)	0.073
Adjusted odds ratio (95% CI)[b]	1.14 (0.97-1.35)	1.0 (reference)	0.115

95% CI=95% confidence interval

[a]Model adjusted for gender

[b]Model adjusted for gender, baseline Kellgren and Lawrence grade, and baseline KOOS pain subscale score

FIGURE LEGENDS

Figure 1. Study flowchart

Figure 2. Change in normalized quadriceps (a) and hamstrings (b) peak torque (involved leg) for the exercise therapy (ET) and arthroscopic partial meniscectomy group (APM)

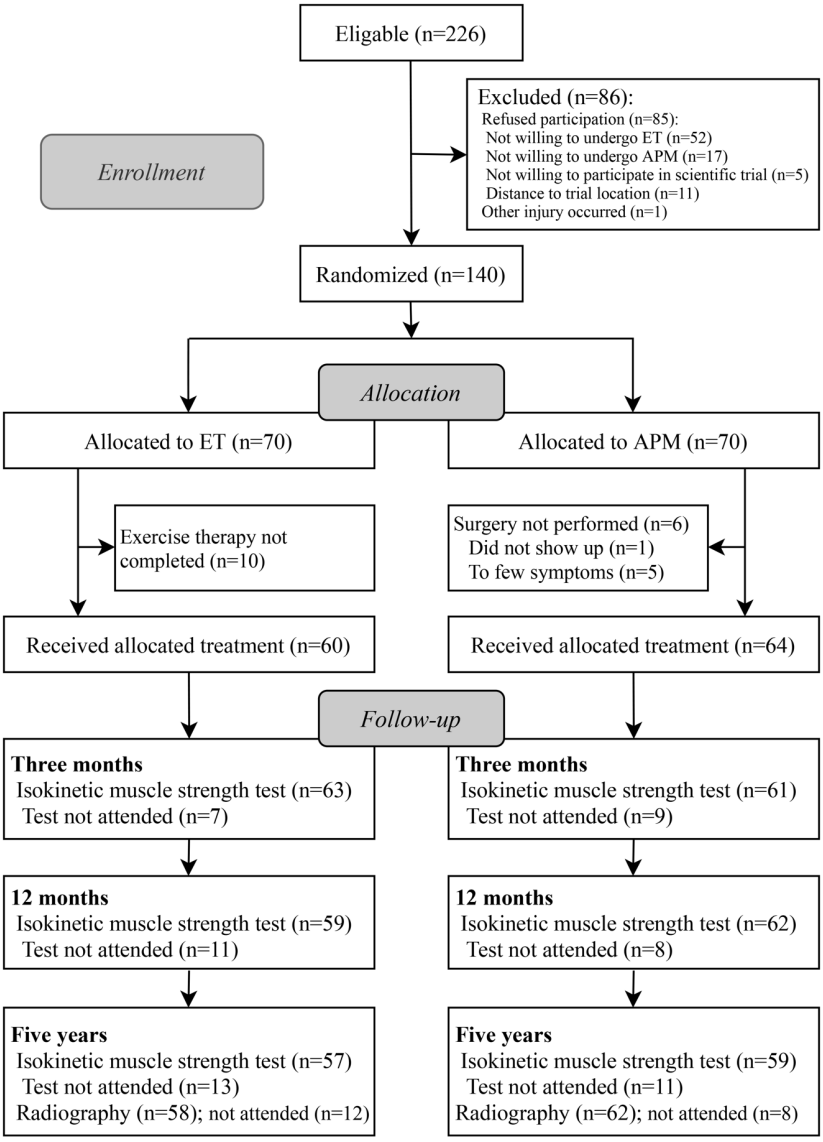

Figure 1. Study flowchart

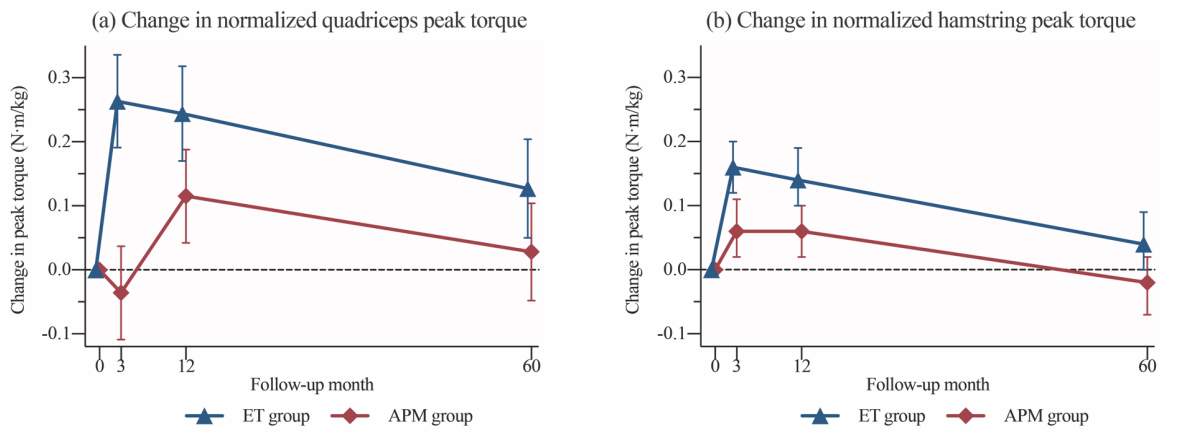

Figure 2. Change in normalized quadriceps (a) and hamstrings (b) peak torque (involved leg) for the exercise therapy (ET) and arthroscopic partial meniscectomy group (APM)

Supplementary Table 1. Proportion of responders[1] at each follow-up in the exercise therapy (ET) and arthroscopic partial meniscectomy APM group

	3 months					**12 months**					**5 years**				
	ET		APM		P-value	ET		APM		P-value	ET		APM		P-value
Quadriceps	**<15%**	**≥15%**	**<15%**	**≥15%**		**<15%**	**≥15%**	**<15%**	**≥15%**		**<15%**	**≥15%**	**<15%**	**≥15%**	
Peak torque (N·m/kg)	35	28	51	10	<0.001	34	25	46	16	0.054	41	16	47	12	0.331
	(55.6)	(44.4)	(83.6)	(16.4)		(57.6)	(42.4)	(74.2)	(25.8)		(71.9)	(28.1)	(79.7)	(20.3)	
Total work (J/kg)	40	22	55	6	<0.001	37	22	44	18	0.335	42	15	47	12	0.446
	(64.5)	(35.5)	(90.2)	(9.8)		(62.7)	(37.3)	(71.0)	(29.0)		(73.7)	(26.3)	(79.7)	(20.3)	
Hamstrings	**<20%**	**≥20%**	**<20%**	**≥20%**		**<20%**	**≥20%**	**<20%**	**≥20%**		**<20%**	**≥20%**	**<20%**	**≥20%**	
Peak torque (N·m/kg)	41	22	50	11	0.033	39	20	50	12	0.070	44	13	53	6	0.066
	(65.1)	(34.9)	(82.0)	(18.0)		(66.1)	(33.9)	(80.6)	(19.4)		(77.2)	(22.8)	(89.8)	(10.2)	
Total work (J/kg)	39	23	51	10	0.010	34	25	51	11	0.003	43	14	55	4	0.008
	(62.9)	(37.1)	(83.6)	(16.4)		(57.6)	(42.4)	(82.3)	(17.7)		(75.4)	(24.6)	(93.2)	(6.8)	

Values are numbers (%)

[1]=Change in normalized quadriceps strength of ≥15% or in normalized hamstrings strength of ≥20%

N·m/kg=Newton meter/kilograms; J/kg=Joule/kilograms

Supplementary Table 2. Estimated absolute knee muscle strength at follow-ups for the exercise therapy (ET) and arthroscopic partial meniscectomy (APM) group

	3 months		**12 months**		**5 years**	
	ET (n=63)	APM (n=61)	ET (n=59)	APM (n=62)	ET (n=57)	APM (n=59)
Quadriceps						
Peak torque (N·m/kg)						
Involved	2.22 (2.09, 2.34)	1.99 (1.86, 2.12)	2.20 (2.07, 2.32)	2.14 (2.02, 2.26)	2.08 (1.97, 2.19)	2.05 (1.95, 2.16)
Uninvolved	2.35 (2.24, 2.45)	2.29 (2.18, 2.39)	2.32 (2.22, 2.43)	2.28 (2.18, 2.39)	2.04 (1.93, 2.15)	2.09 (1.98, 2.20)
Total work (J/kg)						
Involved	10.61 (9.99, 11.23)[1]	9.50 (8.88, 10.12)	10.68 (10.06, 11.29)	10.21 (9.60, 10.81)	10.06 (9.49, 10.62)	9.99 (9.43, 10.55)
Uninvolved	11.05 (10.54, 11.57)[1]	10.72 (10.21, 11.24)	11.17 (10.65, 11.68)	10.82 (10.30, 11.33)	9.84 (9.29, 10.38)	10.14 (9.60, 10.68)
Hamstrings						
Peak torque (N·m/kg)						
Involved	1.18 (1.11, 1.24)	1.17 (1.10, 1.23)	1.16 (1.09, 1.23)	1.16 (1.10, 1.23)	1.06 (1.00, 1.12)	1.08 (1.02, 1.14)
Uninvolved	1.20 (1.14, 1.25)	1.18 (1.12, 1.24)	1.20 (1.14, 1.26)	1.18 (1.12, 1.24)	1.05 (0.99, 1.12)	1.07 (1.01, 1.14)
Total work (J/kg)						
Involved	6.50 (6.07, 6.93)[1]	6.45 (6.02, 6.88)	6.37 (5.93, 6.80)	6.48 (6.05, 6.91)	5.80 (5.37, 6.24)	5.95 (5.52, 6.39)
Uninvolved	6.58 (6.20, 6.96)[1]	6.58 (6.20, 6.96)	6.66 (6.28, 7.04)	6.65 (6.27, 7.03)	5.65 (5.25, 6.06)	6.04 (5.64, 6.44)

Values are means (95% confidence interval)

N·m/kg=Newton meter/kilograms; J/kg=Joule/kilograms

[1]n=62

Supplementary Table 3. Baseline characteristics for participants with and without radiographic knee osteoarthritis progression

Characteristics	Progressors (n=65)	Non-Progressors (n=55)
Gender, men	37 (56.9)	37 (67.3)
Age (years)	49.4 (6.2)	49.8 (6.3)
Body mass index (kg/m^2)	26.6 (4.1)	25.3 (3.5)
KOOS pain	62.3 (18.0)	70.5 (15.8)
Treatment group, exercise therapy	31 (47.7)	27 (49.1)
KL grade		
Grade 0	52 (80.0)	34 (61.8)
Grade 1	11 (16.9)	19 (34.5)
Grade 2	2 (3.1)	2 (3.6)
Quadriceps peak torque (N·m/kg)		
Men	2.08 (0.53)	2.39 (0.49)
Women	1.53 (0.44)	1.87 (0.38)
Hamstrings peak torque (N·m/kg)		
Men	1.16 (0.31)	1.23 (0.25)
Women	0.85 (0.24)	0.97 (0.22)

Values are means (SD) or numbers (%)

KOOS=Knee Injury and Osteoarthritis Outcome Score; KL=Kellgren and Lawrence classification; N·m/kg=Newton meter/kilograms

Name of candidate: Bjørnar Berg

Title of thesis: Long-term consequences of degenerative meniscal tears in middle-aged patients

Abbreviations for different types of corrections:

Cor – correction of language

Cpltf – change of page layout or text format

Page	Para	Line	Original text	Type of correction	Corrected text
23	2	4	… six to 12 weeks, were performed …	Cor	… six to 12 weeks, exercises were performed …
29	2	1	Figure 2 describes…	Cor	Figure 3 describes…
32	3	9	… rotation (Figure 4).	Cor	… rotation (Figure 5).
35	2	2	… in five grade, …	Cor	…in five grades, …
50	2	6	... group allocation.	Cpltf	... group allocation.[33]
55	3	7	… underlaying …	Cor	… underlying …
59	1	8	… preclude …	Cor	… precluded …
61	3	7	…, improved clinically relevant …	Cor	…, showed clinically relevant improvements …
63	3	4	… atherogenic …	Cor	… arthrogenic …
64	3	6	… presences …	Cor	… presence …
66	3	1-2	Both APM and exercise therapy improved patient-reported pain and knee function clinically relevant, …	Cor	For both APM and exercise therapy, improvements in patient-reported pain and knee function were clinically relevant, …
66	4	1-2	… exist in individuals with	Cor	… have been identified in individuals with …