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Published in:
The American journal of sports medicine

DOI:
10.1177/0363546507307396

2007

LUND UNIVERSITY
Faculty of Medicine

Am J Sports Med 2007

Clinical Sports Medicine Update

The Long-Term Consequence of ACL and Meniscus Injuries: Osteoarthritis

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ABSTRACT

Objectives: To review the long-term consequences of injuries to the ACL and menisci, the pathogenic mechanisms, and the causes of the considerable variability in outcome.

Injuries of the ACL and menisci are common in both athletes and the general population. At 10-20 years after the diagnosis, on average 50 % of those diagnosed with an ACL or meniscus tear have OA with associated pain and functional impairment: the young patient with an old knee. These individuals make up a substantial proportion of the overall OA population. There is a lack of evidence to support a protective role of repair or reconstructive surgery of the ACL or meniscus against OA development. A consistent finding in a review of the literature is the often poor reporting of critical study variables, precluding data pooling or a meta-analysis.

Osteoarthritis development in the injured joints is caused by intra-articular pathogenic processes initiated at the time of injury, combined with long-term changes in dynamic joint loading. Variation in outcome is reinforced by additional variables associated with the individual such as age, sex, genetics, obesity, muscle strength, activity and re-injury. A better understanding of these variables may improve future prevention and treatment strategies. In evaluating medical treatment we now expect large randomized clinical trials (RCT) complemented by post-marketing monitoring. We should strive towards a comparable level of quality of evidence in surgical treatment of knee injuries. In instances where an RCT is not feasible, natural history and other observational cohort studies need to be as carefully designed and reported as the classical RCT, in order to yield useful information.

Key terms: ACL, meniscus, rupture, outcome, osteoarthritis

Injuries to the ACL and menisci frequently occur in athletes. Although ACL ruptures occur less commonly in the general population, meniscal lesions are common in both athletes and in the general population.[44-45,47-52,87,100] There is ample evidence that on long-term follow-up these lesions are associated with the development of knee osteoarthritis (OA), leading to pain and functional impairment already in the young or middle-aged adult: “the young patient with an old knee”. Symptomatic OA in these young patients remains a profound and largely unsolved treatment challenge. There is insufficient evidence to prove that surgical treatment of ACL or meniscal lesions is able to diminish future development of knee OA. A consistent finding in our review of the literature was the often poor reporting of critical study variables, preventing a formal meta-analysis. Against this background it is pertinent to review our current understanding of the long-term consequences of these injuries and the causes of outcome variability, the mechanisms that may be involved in the development of OA in the injured knee, and how a better understanding of these mechanisms may influence future prevention and treatment strategies.

INCIDENCE OF ACL AND MENISCUS INJURIES

The ACL is the most commonly disrupted knee ligament, but isolated ACL tears are uncommon. Rather, associated injuries to the menisci, other ligaments, joint cartilage and subchondral or cancellous bone are often observed. The pattern of associated injuries may be influenced by the mechanism and force of the trauma causing the ACL rupture. It is likely that these associated injuries significantly contribute to the risk of future OA developing after an ACL injury.

ACL injuries most commonly occur in athletes and the physically active.[10] A number of studies have reported on the frequency of ACL tears in different types of sports activities. In professional soccer, a risk increase has been estimated of between 100 and 1000.[38,69] The highest incidence is seen in adolescents playing sports that involve pivoting, such as football, soccer, basketball, and team handball. Young women have a 3-5 times higher risk of this injury than men when participating in these sports.[5,53,65,98,120,137,146,159]

The population incidence of ACL injury is less well studied. Based on an in-hospital clinical diagnosis of ACL rupture, the annual incidence was reported to be 30 per 100 000 in Denmark.[123] However, an almost threefold higher annual incidence of 81 per 100 000 for the ages between 10 and 64 in the general population in Sweden was recently shown.[61] This latter report was based on the subacute magnetic resonance imaging (MRI) examination of all cases presenting at a hospital emergency room with an acute rotational trauma associated with effusion, and is less prone to have missed ACL ruptures due to clinical misdiagnosis. However, even this higher number is based only on those patients seeking health-care and who are referred to the emergency room, and is therefore likely an underestimate of the true population incidence of ACL ruptures. In a recent US community based cohort study, the prevalence of ACL tear (MRI diagnosis) was 4.8% among ambulatory individuals aged 50-90 unselected for knee or other joint problems, in line with the higher incidence rates reported from Sweden.[46,61]

An annual incidence of 81 ACL ruptures per 100 000 translates into more than 5 000 ACL ruptures per year in Sweden between the ages 10 and 64. In comparison, Swedish national statistics reports some 3 000 surgical ACL reconstructions per year,[163] consistent with about 50 % of all ACL ruptures in Sweden being reconstructed. This may be compared with 107 000 ACL reconstructions in the USA reported for 1996, and likely higher today.[128]

Meniscal injuries frequently accompany an ACL tear, and every second acute ACL injury is associated with a meniscal lesion.[21,31,125] The proportion of meniscus injuries increases over time in the ACL deficient knee.[26,44,56,59,115,124]

The incidence of symptomatic isolated meniscal tears is less well known and more difficult to ascertain. The previously quoted in-hospital study reported the annual population incidence to be 70 per 100 000 in Denmark,[123] or about 2.5-fold higher than for ACL tears in the same study. However, meniscal injuries are far more likely to be under-reported and under-diagnosed than ACL injuries. In Sweden, some 20 000 meniscus surgeries are done annually, or 8 times the number of ACL reconstructions, suggesting that the true population incidence of symptomatic meniscal lesions is far higher than that reported from Denmark.

These approximations of annual population incidence in turn suggest that the cumulative population risk of an ACL injury between the ages of 10 and 64 is at least 5 % based on MRI examination of the acutely injured knee, and could be considerably higher. The cumulative risk of a meniscus injury leading to surgery in the same age range may be at least 15 %, to which should be added meniscal lesions not diagnosed or not treated by surgery. These estimates, although crude, serve to illustrate the magnitude of a clinical problem where multiple reports show that 10-20 years after the ACL or meniscus tear every second patient has OA, often with significant pain, functional limitations and diminished quality of life.

OSTEOARTHRITIS

Osteoarthritis describes a common, age-related, heterogeneous group of disorders characterized by focal areas of loss of articular cartilage in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change and synovitis. These

structural changes are in their more advanced stages visible in the plain radiograph as joint space loss, osteophytes, subchondral sclerosis and bone cysts.[171] They are usually but not always associated with varying degrees of pain, stiffness and functional impairment, with the combination of radiographic change and symptoms fulfilling the criteria for symptomatic OA[1]. Magnetic resonance imaging allows the examination of OA joint changes in more detail, and has added bone marrow lesions (BML), synovial changes, capsule thickening and meniscal maceration and extrusion to the list of imaging pathology associated with OA.[135] Both joint changes and symptoms progress slowly over years. Structural changes consistent with incipient OA can be found in joints by, e.g., arthroscopy or MRI long before they fulfill the classic criteria of OA, in line with the common existence of structural joint changes with no or only intermittent symptoms and the limited association between structural changes and symptoms in OA (Fig. 1).[35]

Osteoarthritis has generally been thought of as a progressive condition. However, several studies suggest that this is not always the case.[33,34,131,148] The natural history of early-stage structural joint changes, or the extent to which they predict the development of full-blown symptomatic OA, is only sparsely documented.[14,15,22,36,79,80,121,155]

Risk factors of joint damage and progression

The joint changes in OA are caused by a blend of systemic factors that predispose to the disease, and by local mechanical factors (including trauma and loading) that determine its distribution and severity (Fig. 2). The mechanisms leading to cartilage loss are well described, but less is known about the pathogenesis of the concomitant bone and soft-tissue changes.[35] In

[1] Unless otherwise stated, osteoarthritis (OA) when used in this review refers to the combination of structural joint change and symptoms.

addition to age, the main risk factors for radiographic changes include a family history, developmental conditions that affect joint growth or shape, joint injuries, certain work or leisure activities, muscle weakness, and obesity.[54,82,143,156] A number of gene variations have been described as being associated with OA, but most 'sporadic' OA probably depends on minor contributions from variations in several different genetic loci.[104,105,168]

The common classification of OA into primary and secondary OA cannot be maintained. Osteoarthritis is a multifactorial disease with genetic and environmental determinants (Fig. 2). All cases are influenced by both genetics and environment, with the weight of causes forming a continuum between the extremes of predominantly genetic or predominantly environmental. For example, the risk of 'post-traumatic OA' after a meniscal injury of the knee is strongly influenced by the presence of finger OA (a marker of the presence of heredity for generalized OA), by obesity, and by sex.[37,48,50] Moreover, MRI based studies show that meniscus and ligament lesions, traditionally associated with 'secondary' OA, are much more common in 'primary' knee OA than was previously thought, in support of an important role of such lesions in what was previously termed 'primary OA'.[2,8,15,25,44,45,46,49,73,80,87] Continued exploration of gene-environment interactions in OA may be helpful for our understanding of both the causes and courses of OA.[81,85] The presence of subtle genetic variations in the individual may provide a 'permissive environment' for environmental risks such as joint loading or injury to present as an OA phenotype.

Pathogenesis of joint damage and joint pain

Changes in joint cartilage associated with OA include a gradual proteolytic degradation of the matrix, associated with increased synthesis of matrix components by the chondrocytes.[71,150]

These events on the molecular level are reflected by the early morphological changes of cartilage swelling, surface fibrillation, cleft formation and later loss of cartilage volume. Concomitant events in bone are less well understood, but include the development of osteophytes at the joint margin through ossification of cartilage outgrowths, and changes in the vascular supply, turnover and structure of the subchondral bone.[20,112,172] Cytokines and other signaling molecules released from the cartilage, synovium and bone affect the function of chondrocytes and cells of other joint tissues, including the meniscus. Osteoarthritis has been regarded as a non-inflammatory arthritis, but improved detection methods show that inflammatory pathways are up-regulated.[1] Several of the environmental risk factors mentioned (obesity, joint injury, work or leisure related joint overload) are mechanical, and recent studies have stressed the importance of muscle weakness, joint instability and malalignment as possible causes of OA.[76,153,154,157,166]

Osteoarthritic joint damage may be associated with activity-related joint pain and functional impairment. Since cartilage is aneural it cannot be the tissue that directly generates pain. Current work suggests that the subchondral bone and synovium are responsible for nociceptive stimuli, and that peripheral neuronal sensitization is an important feature in OA pain.[18,29,55,111,173] Central pain sensitization may also occur, and psychosocial factors are important determinants of pain severity in OA. The simple concept of a direct link between joint damage and symptoms in OA is therefore inconsistent with available evidence. Rather, the evidence favors a complex interaction between local events in the injured or OA joint, muscle weakness, pain sensitization, the cortical experience of pain, and what people do in their everyday lives.[35,109,127,162]

Outcomes in OA

Outcomes in OA are expressed at multiple levels, and measurements applied in OA studies need to recognize these multiple dimensions. They include

1) patient-relevant outcomes [patient-centered and patient-reported measures of e.g. pain and function][63,89,136,141]
2) structural measures [plain radiography, MRI or arthroscopy][27,28,42,88,134]
3) biochemical markers [molecular process markers, or tissue function markers such as measures of cartilage biomechanics][7,93,99,102,169]

Patient-relevant outcomes remain the gold-standard in monitoring disease or results of disease interventions, against which other outcome measures may be compared and validated.[30] Numerous outcome measures have been developed for use in knee joint injury and in knee OA, with a varying extent of validation in the relevant patient populations ranging from short- to long-term outcomes.[63]

Radiographic measures have traditionally been used as outcomes in studies on progression of OA. However, for radiography relation with patient-relevant outcomes and sensitivity to change are limited.[68] Standardization of image acquisition and assessment is critical.[27,88] MRI visualizes additional joint structures, may be able to monitor some aspects of tissue composition, and may be more sensitive to change.[42,134,138,140]

Biochemical markers are generated by metabolic processes in the injured or OA joint. The active processes in the joint, involving changes in both synthesis and degradation, result in the altered release of matrix molecules, proteolytic molecular fragments, and other molecules involved in their altered metabolism such as proteases, cytokines, chemokines, and growth factors. Products released into the synovial compartment may be removed from there by

capillary and lymphatic flow to appear in the blood circulation, and in some cases they may survive metabolism and appear in the urine after further processing by the kidneys.[7,93,94,99]

These different dimensions of outcome are all related to the concept of defining an endpoint when measuring disease development after joint injury or in OA, or in a clinical trial when comparing two different treatments. In the greater context of treatment of a human medical condition, how a patient feels, functions or survives is the most relevant outcome. Other measures and endpoints may be relevant as well, but need to be validated against this gold standard. For an outcome using e.g. imaging, clinical examination or a biochemical marker to be validated as a surrogate endpoint, it must be shown that its measurement can serve as a reliable substitute for, or predict, a clinically meaningful endpoint.[30] A *clinical endpoint* may be defined as a characteristic or variable that measures how a *patient* feels, functions or survives. A challenge in the validation of any surrogate marker is that its measurement may not take into account adverse events, since the processes associated with an adverse event may not be monitored by the marker. Such adverse events may nullify all or some of the treatment benefit. Further, a surrogate measure may not register all beneficial effects of treatment if these are not in the pathway of the measure. Methods involving measures of joint structure, joint stability, biochemical markers, cartilage biomechanics, etc. are in different stages of development, but none of them can be said to have been sufficiently validated as a surrogate for the clinically relevant outcome: how the patient feels, functions or survives.

An example of particular relevance to the topic of this review may be given. In studies of ACL injured subjects static joint laxity is a frequently reported outcome, and comparisons made between different surgical techniques, over time, and in comparison with those not operated on. However, knee laxity, just like structural outcomes of OA, correlates poorly with symptoms, function or dynamic stability.[68,132,151,158,162,167]

ACL INJURIES AND OA

Given that a majority of patients diagnosed with an acute ACL tear are below 30 years of age at the time of injury, and many of them below 20, ACL injuries are responsible for a large number of individuals with early-onset OA with associated pain, functional limitations and decreased quality of life already in the ages between 30 and 50.[98,170] They are the 'young patients with old knees'.

Long-term outcomes after ACL rupture

Radiographic signs of OA - The reported rates of OA after an ACL injury vary between some 10 and 90 % at 10 to 20 years after the ACL injury.[64,100,119] Stating an average OA rate is difficult due to the great variability of the reported results, but an overall long-term average of more than 50 % may be suggested (Fig. 3). The data points provided in Figure 3 each represent a discrete data set as reported in 127 individual papers of follow-up after ACL rupture and or surgery published from the 1970s to 2007. If a report contained information on radiographic outcome of more than one form of treatment, each was represented by a data point in the figure. Publications were identified in MedLine using the search terms 'anterior cruciate ligament', 'injury', 'osteoarthritis', 'follow-up'. Additional papers were identified through the reference lists of these publications. A final selection was made based on interpretable radiographic data. At least 10 different methods for grading radiographic OA were used, few of them well described or validated. A best effort was made to translate the data into the accepted Kellgren and Lawrence scale.[84] Study group size varied from about 10 to 1000, loss to follow-up from 0 to 90 %, sex distribution from 0 to 100 % males, age at

injury and surgery from about 10 to older than 50 years, proportion of associated injuries from low to high. In comparison with a similar data summary published in 1994,[100] the increase in number of data points is notable, as well as the continued lack of evidence of ACL reconstruction providing protection against long-term joint damage. As already commented on, structural joint damage is only one aspect of joint injury outcome, and additional dimensions of outcome are discussed below.

Ideally, all the study variables mentioned above (and more), and an overall methodological quality rating of each report should be used to weight the numbers presented in each study. However, a consistent finding when reviewing these publications was the often poor reporting of many critical study variables, making a formal meta-analysis or pooling of data of either structural or patient-centered outcomes impossible. Our conclusion in this respect is consistent with that of other recent reviews of the field.[12,91]

Symptoms and function – A large number of studies have reported on symptom and function outcomes of ACL tear and reconstruction, but few of them extend beyond 10 years of follow-up.[10,11] Many different outcome measures have been used, further increasing the difficulties of performing a formal meta-analysis, in addition to the difficulties created by the other aspects of study heterogeneity discussed above. In an attempt to summarize long-term outcome for the purpose of this review, we extracted Lysholm score data from 54 publications on ACL rupture treated with or without reconstruction.[165] The great majority of studies using the Lysholm score presented group average follow-up values around 90, being classified as good or excellent (Fig. 4). There was no apparent time-dependent trend of outcome versus follow-up. The Knee injury and Osteoarthritis Outcome Score (KOOS) being a more recent measure provided data from 8 publications.[142] In particular the KOOS subscales 'Sport and Recreation' and 'Quality of Life' showed marked changes over time (Fig. 5), suggesting that

if monitored by valid patient-administered outcome measures, results of ACL rehabilitation and or surgery are at best at 1-2 years of follow-up, and then gradually deteriorate over time. At 12 years after an ACL rupture 75 % of female soccer players reported having significant symptoms affecting their knee-related quality of life, and 42 % were considered to have symptomatic radiographic knee OA.[98] In a corresponding cohort study of male soccer players with an ACL tear, similar consequences on joint structure and symptoms were reported 14 years after injury.[170] There was no difference in outcome in either study between those who had been treated with surgical ACL reconstruction and those who had not. The mean age of these former athletes at follow-up was 31 years for the women and 38 years for the males. In many individuals this injury leads to the development of OA with associated knee-related symptoms that severely affect the quality of life of the young individual.

MENISCUS INJURIES AND OA

While the majority of patients with an acute ACL injury are below 30 years of age, the age distribution of those diagnosed with an isolated symptomatic meniscus lesion is different, being very broad and with a group mean age around 35 years.[48,50,52,145] A further analysis based on the type of meniscus tear revealed that the mean age of those diagnosed with longitudinal tears, often characterized as traumatic in origin, was about 30, while those diagnosed with degenerative tears often had a mean age of about 40 years.[52,145] Joint cartilage damage was a more common finding in individuals with degenerative tears.[9,25,48]

Long-term outcome after meniscus tears

Radiographic signs of OA - Similar to publications on ACL injuries, reports on OA prevalence after meniscus tears and surgery provide widely different frequencies of radiographic OA (Fig. 6). Overall, some 50 % of those meniscectomized 10-20 years earlier are reported as having radiographic knee OA, or an odds ratio of about 10 compared with a reference group of the same age and sex distribution without known knee injury. The significantly increased OA risk associated with a meniscus tear and surgery is consistent with the important role proposed for an intact meniscus in the ACL deficient knee.[113] While some reports suggest a lower rate of radiographic OA after partial meniscal resection than after total or subtotal,[48,51] the 'big picture' given by the data distribution in Fig. 6 fails to provide supportive evidence. Similar to Fig. 3, each data point in Fig. 6 represents a discrete data set as reported in an individual publication of follow-up after a surgically treated isolated meniscus tear. The 41 publications were identified in MedLine using the terms 'meniscus', 'injury', 'osteoarthritis', 'follow-up'. For further details, see Fig. 3. As for reports on ACL injury follow-up, there were large variations in study group size, loss to follow-up, age, sex distribution, etc., and an overall paucity of critical study design details.

Symptoms and function – More recent reports with improved design and sufficient statistical power confirm that meniscal lesions and subluxations are associated with a high risk of cartilage loss and progression of existent OA.[80,138] Some 15-20 years after meniscectomy about 50 % of the patients have OA, with both symptomatic and radiographic outcome being worse for those diagnosed with a degenerative meniscus tear at index arthroscopy (Fig. 7).[48,50,51,52] Similar to patients at 12-14 years after an ACL tear (Fig. 5), the aspects of patient-relevant outcome most severely affected at 14 years after isolated meniscus resection were the KOOS subscales 'Sports and Recreation', and 'Knee related Quality of Life' (Fig. 7). The

mean age at follow-up for these individuals was 54 years, and at this age their subscale values were significantly worse than for an age-matched reference group (Fig 7). Of note is that those with an isolated degenerative meniscal tear had KOOS values comparable with those with an ACL tear (Fig. 7), given the same time of follow-up.

The outcome after isolated meniscus resection was worse for women, for obese subjects, and for those with a lateral meniscus resection. Interestingly, patients with a unilateral isolated meniscectomy had not only a significantly increased risk of OA in the operated index knee but also in the non-operated, non-injured contralateral knee, albeit to a lesser degree.[48] Of further note was that the meniscectomized patients who also had finger joint OA were shown to have a higher risk of knee OA following meniscectomy than those without finger OA.[50]

Meniscus tear population contains subgroups - These observations suggest that the population with isolated meniscal tear is heterogeneous, consisting of at least two major subgroups. Those with a longitudinal tear may be regarded as often having a traumatic tear in a previously healthy meniscus and healthy knee. The long-term outcome for this group would be expected to be influenced by the same factors as for ACL tears, as discussed above. In contrast, the available evidence strongly suggests that degenerative meniscal tears, often following insignificant trauma, generally occur in knees already compromised by changes that may represent incipient OA or even overt OA.[25,47,48,87,103,145] These individuals likely represent a population subgroup with a generally increased risk for OA onset at a young age, including OA in their contralateral knee and their finger joints, and the degenerative meniscal tear may be an incidental finding on knee MRI and a first signal feature of their knee OA. The long term radiographic and symptom outcome of those with degenerative tears was worse than for those with traumatic tears (Fig. 7).[48,51,52] It may therefore not be surprising that treatment of patients with these types of meniscus lesions by arthroscopic debridement or

meniscus resection is no more effective than lavage, sham surgery, or non-surgical treatment.[24,72,117] An arthroscopic partial resection of the degenerated meniscus or removal of damaged cartilage will do little to influence the disease processes in the OA joint, or alleviate symptoms that likely originate from other structures of the joint than the cartilage or meniscus.[161] Added to these challenges is the difficulty of making an accurate clinical diagnosis of the type of meniscal tear.[32] Our review of the literature did not provide support of meniscal suture or meniscal allograft treatment protecting the knee against future OA development (Fig. 6).

DISCUSSION

Causes of variability in outcome and development of OA after ACL and meniscus tears

Why is there such a wide variation in reported rate of OA after an ACL or meniscus injury? Explanations (Fig. 8) may be divided into those associated with

1) the injury
    a) acute events at the time of trauma
    b) later events such as reconstructive surgery, rehabilitation, return to sport, chronic instability, and later associated injuries
2) the individual
    a) including activity level, muscle strength, body mass index, personality and education

3) the methods and criteria used to ascertain OA and evaluate through different outcome measures its consequences on the patient, with bias being introduced on different levels

The injury - The acute injury mechanisms leading to an ACL rupture are well studied but only in part understood.[3,5,6,65] ACL tears rarely occur in isolation but are in at least 50% of the acute cases associated with other ligament sprains, meniscal tears, articular cartilage injuries, bone bruises and sometimes intra-articular fractures.[10,11] The substantial force required to tear a healthy ACL, ligament and meniscus is consistent with the frequent presence of subchondral bone bruises visible on MRI.[121] Such bone bruises, also termed post-traumatic bone marrow lesions, may represent 'foot-prints' of the compressive forces on the joint surfaces at the moment of injury.[70,129,149,175] The natural history of bone marrow lesions, or their possible role for OA development or symptoms, is not well documented. However, even in the absence of visible cartilage injury by inspection or MRI, the presence of a bone marrow lesion suggests that the joint cartilage of the injured joint will have sustained a considerable mechanical impact at the moment of injury. There is evidence that this in itself leads to disruption of the cartilage matrix, chondrocyte death, accelerated chondrocyte senescence and changes in cell metabolism.[19,107] These events are associated with OA development, even in the absence of joint instability.[19] In addition to the direct effects of mechanical overload on cartilage cells, interaction of the chondrocytes with synovial cells will enhance the negative effects on joint cartilage.[133] Finally, intra-articular bleeding is common in connection with these injuries, which in itself will activate inflammatory pathways of the joint with longterm effects.[16,147] Reconstructive ACL surgery will cause additional intra-articular trauma and bleeding, which may be expected to reinforce and prolong an inflammatory response caused by the acute injury.

Biochemical markers have been monitored in joint fluid, blood and urine following injury to the human ACL or meniscus. The results show both an acute and sustained increase in the release of matrix molecular fragments, proteases and cytokines from joint cartilage and other joint tissues.[75,92,95,96,97,101,103,122] These findings are consistent with an acute ACL or meniscus injury within days resulting in a rapid onset of damage to the type II collagen network, aggrecan and other matrix components of the joint cartilage, leading to a weakened matrix molecular network. This may make the joint cartilage less resistant to loading, until endogenous repair mechanisms have been activated. Matrix molecule fragments released may in themselves activate inflammatory pathways. With increasing time after injury biomarker levels generally decrease, but often remain increased for years after injury at levels similar to those in the OA joint, reflecting an increased metabolism in the injured joint.

In addition to the acute events associated with a joint trauma, the lack of a functionally normal ACL or meniscus will change the static and dynamic loading of the knee, generating increased forces on the cartilage and other joint structures.[4,41,160] As a result, additional lesions commonly occur (or become symptomatic) with time in the ACL injured knee, and in particular in the meniscus.[40,57,114] These subsequent lesions may have an important role in the long-term development of OA, and be more frequent in active individuals with a functionally unstable knee. Although current methods of ACL reconstruction go some way towards restoring the mechanics of the knee, the ACL reconstructed knee is not a normal knee.[130,132] Over the course of years following the trauma, the injured knee, reconstructed or not, will be submitted to abnormal loading patterns in everyday activities as well as in sports, significantly increasing the risk of OA. A report based on review of an administrative database suggested that ACL reconstruction in a young and active population provided some protection against additional procedures, compared to those not reconstructed.[40] In support, a non-randomized

controlled trial reported that early-phase non-surgical management resulted in more late-phase meniscal surgery than did early-phase reconstruction.[57]

Return to play is a frequently used but questioned outcome variable after ACL injury and reconstruction, and perhaps there are other criteria by which ACL reconstruction outcome should rather be measured than time to return to sport.[119] The risk of re-injury increases with the athlete returning to pivoting sports, with an increased risk of OA documented in long-term followup.[120,146,159]

The individual – As noted above, long-term studies on knee injuries are very heterogeneous with regard to factors that might be expected to influence outcome, such as age at injury or surgery, time between injury and surgery, proportions of males and females, physical activity levels and other patient-associated variables. The limited size and the design flaws of many studies most often preclude drawing firm conclusions, and prevent a formal meta-analysis or data pooling. Additional variables such as muscle strength and neuromuscular function, personality types, education, and body mass index (BMI) can also be suspected to influence outcome, but are only rarely reported or analyzed.[17,51,52,162] There is no evidence to support the full restoration of neuromuscular function and muscle strength following ACL or meniscal injury, which may further contribute to OA development after knee injury.

For isolated meniscus lesions, it was shown that outcome was worse for women, for the obese, for those with a lateral meniscectomy, and for those with finger joint OA.[48,50] It appears reasonable to suggest that these OA risk factors also interact in patients with ACL injuries.[17,37]

The assessment methods and criteria –The overall lack of standardization of image acquisition and assessment contributes to the variability in reported radiographic outcome.

Structural outcomes such as joint laxity and radiographic changes do not correlate well with patient-relevant aspects such as pain and function. Aggregating these outcomes into one total score will confound interpretation of the results; outcomes need to be reported separately.

Tapper and Hoover, who in 1969 introduced their system for evaluation of symptoms and function following meniscectomy, categorized outcome into four categories: excellent, good, fair, and poor.[164] The approach is appealing and the raw scores of established knee scoring scales are frequently categorized into these same four categories, using arbitrarily chosen cut-off values. The Lysholm scoring scale is commonly used in knee injury.[106] It aggregates function and symptoms into one single score from 0 to 100, worst to best. A cut-off of 84 points is used to categorize a good/excellent outcome.[139] In Fig. 4 Lysholm results were extracted from 54 publications of ACL injury and ACL reconstruction with follow-up times from 1 to 24 years. Only few studies reported a mean Lysholm score below 84, indicating that most patients were categorized as having a good or excellent outcome. Groups with a reported mean score below 84 included those with extra-articular reconstructions,[62,83] synthetic grafts,[118] and revision surgery,[58] procedures associated with worse outcome. But what does a Lysholm score of 84 represent? A patient could have a slight limp, some problems with stairs and some pain and be categorized as excellent/good with a total score of 89 out of 100. Alternatively, a patient could experience frequent instability excluding sports activity, with some pain and yielding a score of 85 and be categorized as having a good/excellent outcome. Most probably the patients themselves would not categorize either of these scenarios as a good/excellent outcome. Categorizing the raw scores of rating scales tend to inflate the result, and the interpretation of categorical data depends on the content of the particular rating scale and the relative weight given to each component that is aggregated into the total score.[152] Avoidance of data generalization remains the optimal method for studying the outcome of

knee injury.[152] Patient-relevant questionnaires should be self-administered, i.e. filled out by the patients themselves in a neutral setting, since operating surgeons and even "unbiased" observers can introduce bias.[74,90,144] Self-administration of the Lysholm score in patients treated with or without reconstruction with BPTB graft (no difference between treatment groups) gave an average Lysholm score below 84,[98,146,170] comparable to or worse than revision surgery, extra-articular procedures or synthetic grafts and where the questions were filled out by the observer (Fig. 4).

In Fig. 7 KOOS data are given for patient groups with ACL injury or meniscal injury. For comparison, Lysholm data are provided when available for the same populations. The KOOS data, presented as a profile of the five separate subscales, gives a more complete picture of the patients' perception of their knee injury and its consequences on their lives. The discriminative ability of the KOOS translates into smaller numbers of patients needed to determine statistically significant differences between groups being compared.

In conclusion, scores aggregating different dimensions into one total score, and applying cut offs for categorization often yield a good or excellent result. These methodological problems contribute to the difficulty of interpreting results of long-term outcome studies.[12,13]

Pathogenic mechanisms, long-term outcome and the relationship between post-injury OA and primary OA

Ruptures of the ACL and menisci initiate in the acute phase a cascade of pathogenic processes that in themselves have been shown to lead to the development of OA. These injuries also lead to chronic changes in the static and dynamic loading of the knee, further contributing to both initiation and progression of OA development. These 'environmental' factors that

include surgery, activity and re-injuries interact with 'endogenous' factors such as age, sex, genetic variations, obesity, etc. (Fig. 2). This multiplicity of influences is a likely contributing reason for the variable rate of development of OA after these injuries.

We have in this review focused on ruptures of the ACL and meniscus caused by or at least associated with an identified joint trauma, albeit sometimes minor. However, recent reports point to the occurrence of ruptures and pathology of both menisci and ACL for which the patient is often unable to identify a specific causative event.[15,45,46,47,48,79,80] We propose that in many cases these ruptures are a feature of the OA disease process.[47-52,87,103] Pathologic changes in all joint tissues, not just the cartilage, are an integral part of OA. Consistent with the emerging picture of both meniscus and ACL lesions being more common than previously thought in both unselected and OA populations, we may need to reconsider the role of ligament pathology in OA development in general. Perhaps the development of ligamentous insufficiency is an integral part of development of some forms of OA, and plays a greater role in development of 'primary' OA than previously considered? If this is the case, we need to reconsider whether there is any reason to maintain the distinction between 'primary' and 'secondary' OA.

Management of the knee-injured patient: does reconstructive surgery decrease OA development?

A majority of American orthopaedic surgeons believe that ACL reconstruction reduces the rate of OA in ACL-deficient knees.[108] But what is the strength of the evidence for a protective role of ACL reconstruction with regard to long-term OA development in the injured knee? The literature review done in connection with our review does not provide evidence that ACL

reconstruction reduces the rate of OA development, or improves the long-term symptom outcome. Our results thus agree with a recent systematic Cochrane review,[91] that concluded "There is insufficient evidence from randomised trials to determine whether surgery or conservative management was best for ACL injury in the 1980s, and no evidence to inform current practice." The authors further stated that "Given this, there is a need for good quality, and well reported, randomised trials evaluating the effectiveness and cost-effectiveness of current methods of surgical treatment versus non-surgical treatment. The follow up of such trials should be at least 10 years so that the long term effects including degenerative changes can be established." Our understanding in 2007 of the effectiveness of ACL reconstruction to influence long-term consequences of ACL rupture is at the same level as in 1994, when a review of the available evidence concluded that "The literature does not lend support to the efficacy of cruciate ligament repair or reconstruction in retarding the progression of osteoarthrosis after knee injury".[100] A graphic illustration of this problem is given in Figure 9, showing reports on radiographic OA following autograft reconstruction of ACL in relation to year of publication. There is no indication of a decreased rate of OA in more recent reports, as compared to earlier studies. Recent publications concur, commenting on the lack of evidence showing a long-term protection of the joint after ACL reconstruction.[23,119] In further support, recent reports noted that the poor methodological quality of the studies available for meta-analysis called into question the robustness of the analyses, emphasizing the lack of convincing evidence on which to draw any conclusions of the effectiveness of current treatments.[12,13] There is a similar lack of evidence to support that meniscus suture or repair prevents longterm development of OA (Fig. 6).[77] Some reports suggest that ACL reconstruction may provide protection against later meniscal surgery.[40,57,114] Although this could be expected to result in a lower rate of OA development, this remains to be shown.

Current surgical therapy is directed towards restoring the mechanics of the knee. The lack of evidence for this surgical therapy to prevent OA development might be explained by an insufficient quality of the published studies, by the surgical reconstruction not yet being good enough, or by the OA process being initiated and driven by other events. Perhaps the pathogenic processes that occur early after injury have a greater role than previously recognized. Were this the case, then the acute injury phase may represent a window of opportunity for future treatment based on preventing a subsequent cascade of destructive processes. Management of the injured patient needs to take into account both short- and long-term consequences of the injury. Our increasing awareness of the seriousness of the latter suggests that more of our attention should directed towards the long-term consequences.

The common occurrence of ACL injuries, their serious long-term consequences, and the lack of evidence for effectiveness of current interventions to prevent subsequent OA, supports an increased attention on injury prevention.[43,65,126] Attention to injury prevention should include prevention of re-injuries of the knee with a ruptured ACL, since e.g. a subsequent tear of the meniscus increases the risk of OA. Information about other factors associated with an increased risk of OA (e.g. obesity, muscle strength, heredity) should also be part of the risk management discussion with the knee injured individual.

A call for improved quality of studies and reports

An all too common finding in reviewing the literature was a low methodological quality and lack of critical study details. Although there was some degree of quality improvement in more recent publications, further significant improvements are needed in order to assess with any degree of certainty the patient-relevant efficacy of our current treatment of these injuries. The

findings of recent randomized clinical trials comparing arthroscopic surgery with other treatments serve as a reminder that all current treatments might not be effective.[72,117]

Natural history and other observational cohort studies can and need to be as carefully designed and reported as the classical randomized clinical trial (RCT) in order to yield useful information. Examples of important design and reporting aspects include but are not limited to: prospective or retrospective design, recruitment period, consecutive patients enrolled or not, information on those not enrolled, inclusion and exclusion criteria, description of setting, description of injuries and symptoms, time between injury and diagnosis and surgery, diagnostic methods and criteria, carefully described and validated outcomes, inter- and intra-observer variability, treatments clearly described including rehabilitation, exact description of randomization and blinding methods if used, sample size estimations, reporting of drop-out rate, comparison of those who completed the study and those who dropped out, methods of statistical analysis, and more.[14,116] The design and completion of RCTs in knee surgery is challenging but not impossible.[24,39,60,66,67,72,86,110,117] In evaluating pharmacological treatment we now expect large RCTs complemented by post-marketing monitoring of new drugs. We should strive towards a comparable level of quality of evidence in surgical treatment of knee injuries through RCTs and other study designs. Prospective, population-based patient registries of ACL injury with high reporting rates[174] will be a valuable complement to improve our care of patients with these common injuries.

Injuries to the ACL and menisci are associated with a high risk of development of osteoarthritis. To show the benefits of our current management of these injuries, we need good quality and well reported long-term randomized trials that evaluate the effectiveness and cost-effectiveness of current methods.

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FIGURE LEGENDS

Figure 1 A large proportion of those with structural OA joint changes have few or no symptoms. Many of those with OA symptoms have limited or no structural joint damage, at least not detectable by plain radiographs. Using today's criteria, those with a combination of joint damage and symptoms are diagnosed with OA. As our means to detect joint damage by e.g. MRI improves, it is likely that OA criteria may change. The natural history of progression from high risk groups into either of these categories is not well understood.

Figure 2 Schematic representation of OA pathogenesis. The disease is initiated and its progression caused by a combination of endogenous and environmental risk factors. Phenotype variability (structure, degree of inflammation, symptoms, etc.) is explained by the particular mix of these factors in the individual.

Figure 3 Scattergram of the proportion of individuals with radiographic OA plotted against time after ACL injury or reconstructive surgery. Each data point represents a data set from one of 127 individual publications. The different radiographic assessment methods were translated into the Kellgren and Lawrence criteria,[84] using as cut-off for the presence of radiographic OA any of the following: joint space narrowing grade ≥2, sum of osteophyte grades ≥2, or a combination of grade 1 joint space narrowing and a grade 1 osteophyte. Compare with figure 1 Lohmander & Roos 1994.[100] Symbols: ● non-surgical treatment, ▼ primary suture or enhancement, ■ reconstruction by autograft, ♦ reconstruction by synthetic graft or allograft.

Figure 4 Scattergram of outcome after ACL injury and ACL reconstruction assessed by the Lysholm score.[165] Each data point represents the mean (or median) Lysholm score at the average time to follow-up of 54 different studies. Symbols: ● intra-articular autograft or no surgery, observer-administered Lysholm score, ▼ intra-articular autograft or no surgery, mail-administered Lysholm questionnaire. ■ extra-articular reconstruction or synthetic graft or revision ACL surgery, observer-administered Lysholm score. The dashed line shows the Lysholm score value of 84, traditionally used as cut-off for good or excellent outcome. Mail-administration of the Lysholm score in ACL-injured men and women treated with or without reconstruction with BPTB graft (no difference between treatment groups) resulted in an average Lysholm score below 84.[98,146,170]

Figure 5 KOOS subscale values plotted against time of followup for 8 different publications reporting on long-term follow-up after ACL injury. Individual KOOS subscale data for patient groups (open symbols). Mean values for KOOS subscales based on reported mean values for patient groups (lines and filled symbols). KOOS subscale symbols: ● Pain, ▲Symptoms ▼ ADL. ■ Sport/Rec, ♦ QOL.

Figure 6 Scattergram of the proportion of radiographic OA plotted against time after diagnosed or treated meniscus lesion. Each data point represents a data set as reported in one of 41 individual publications. Studies shown here contain isolated meniscus lesions only. For a discussion of study and group variability, see text. Different methods for grading radiographic OA were used in the different publications. For criteria of radiographic OA and further details, see

legend figure 3. Symbols: ● total or subtotal meniscus resection, ▼ partial meniscus resection, ■ meniscus repair.

Figure 7 KOOS subscale profiles for ACL and meniscus injury patients. Lysholm data for the same groups are given for comparison. ● 14 years follow-up of patients with traumatic meniscus tear,[52] ● 14 years follow-up of patients with degenerative meniscus tear,[52] ▼ 12 years follow-up of women with ACL rupture,[98] ▼ 14 years follow-up of men with ACL rupture,[170] Δ 3 months follow-up of patients with partial meniscectomy,[142] □ Reference group with no knee injury and no knee OA.[142]

Figure 8 Variables that influence the outcome of an injury to the ACL or meniscus, and the subsequent risk of OA.

Figure 9. Scattergram of the proportion of individuals with radiographic OA after autograft intra-articular reconstruction of the ruptured ACL plotted against year of publication. Each data point represents a data set from one of 65 publications. The line shows linear regression, with 95% confidence interval (broken lines). For further details, see Fig. 3.

Figure 1

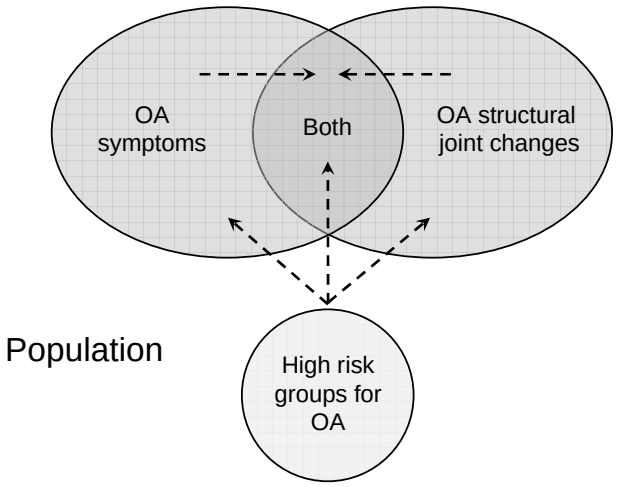


Figure 2

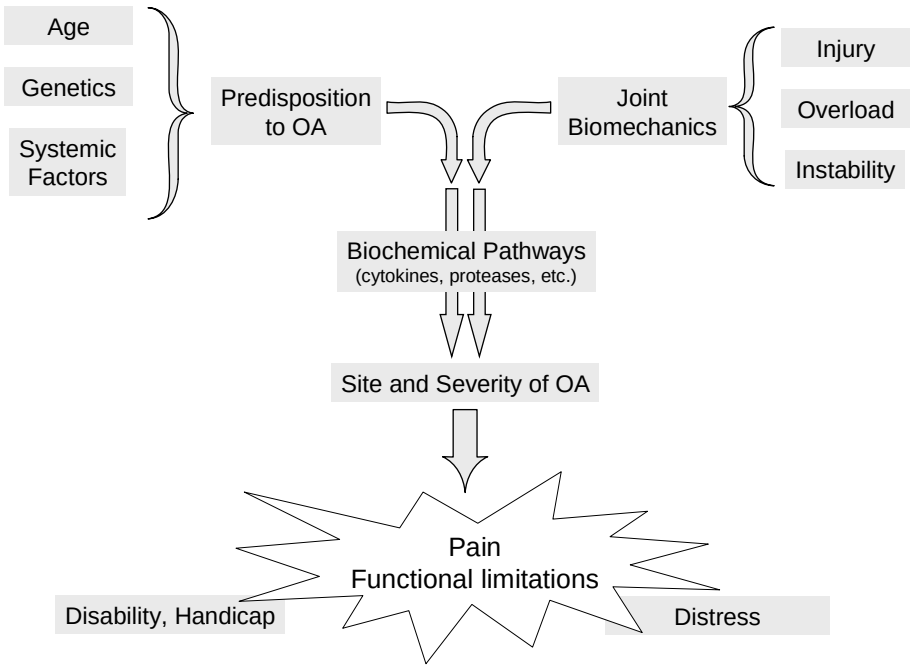


Figure 3

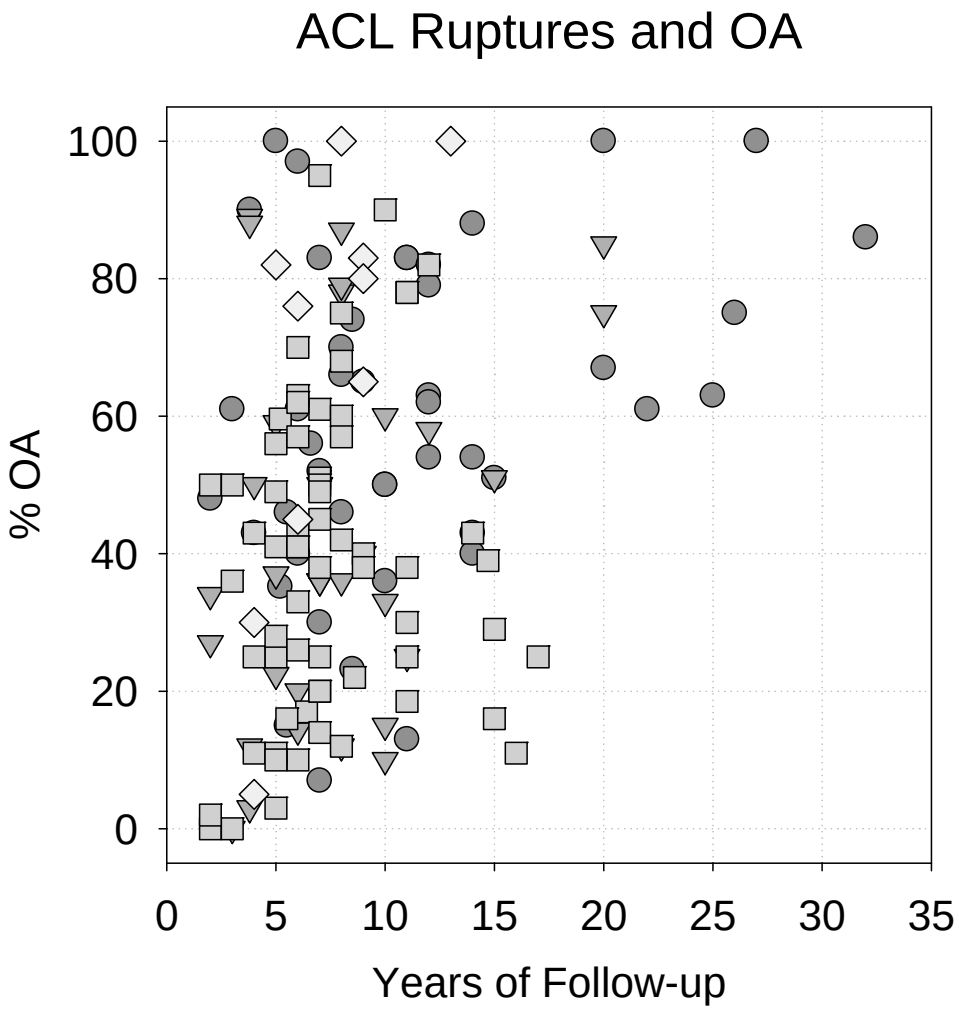

ACL Ruptures and OA
% OA
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Years of Follow-up

Figure 4

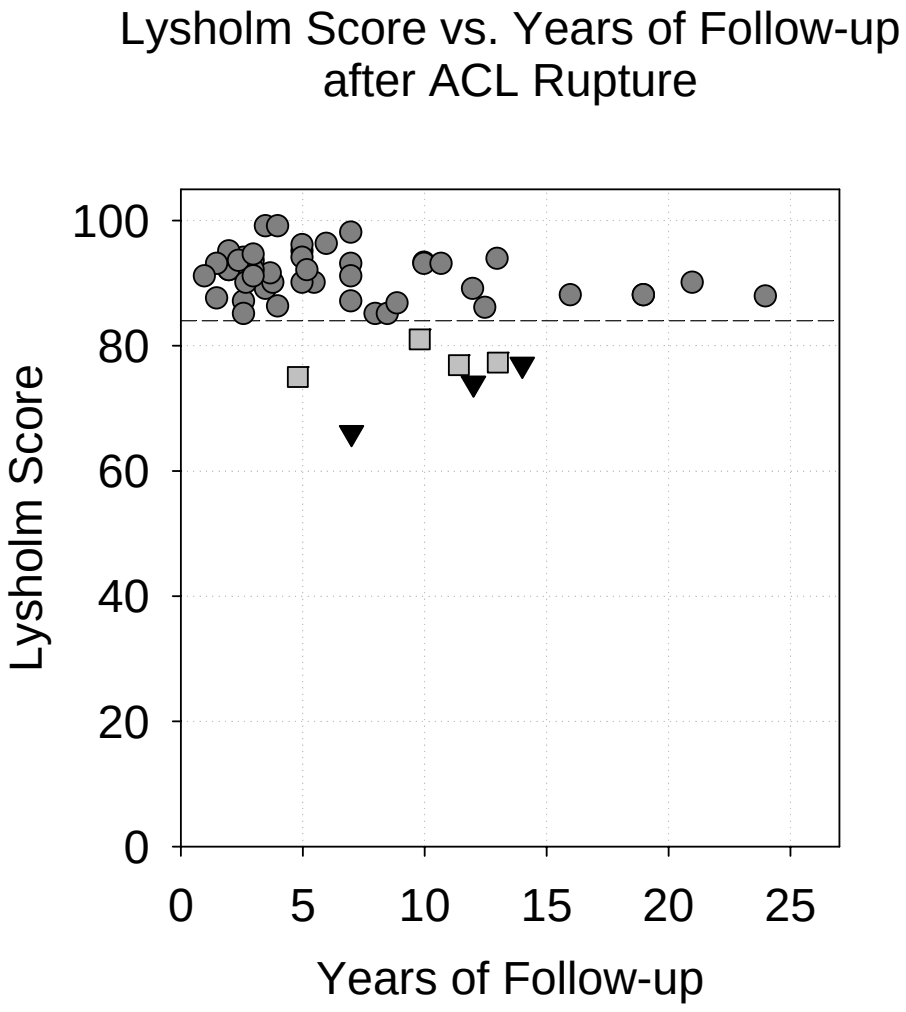

Lysholm Score vs. Years of Follow-up after ACL Rupture
Lysholm Score
100
80
60
40
20
0
0
5
10
15
20
25
Years of Follow-up

Figure 5

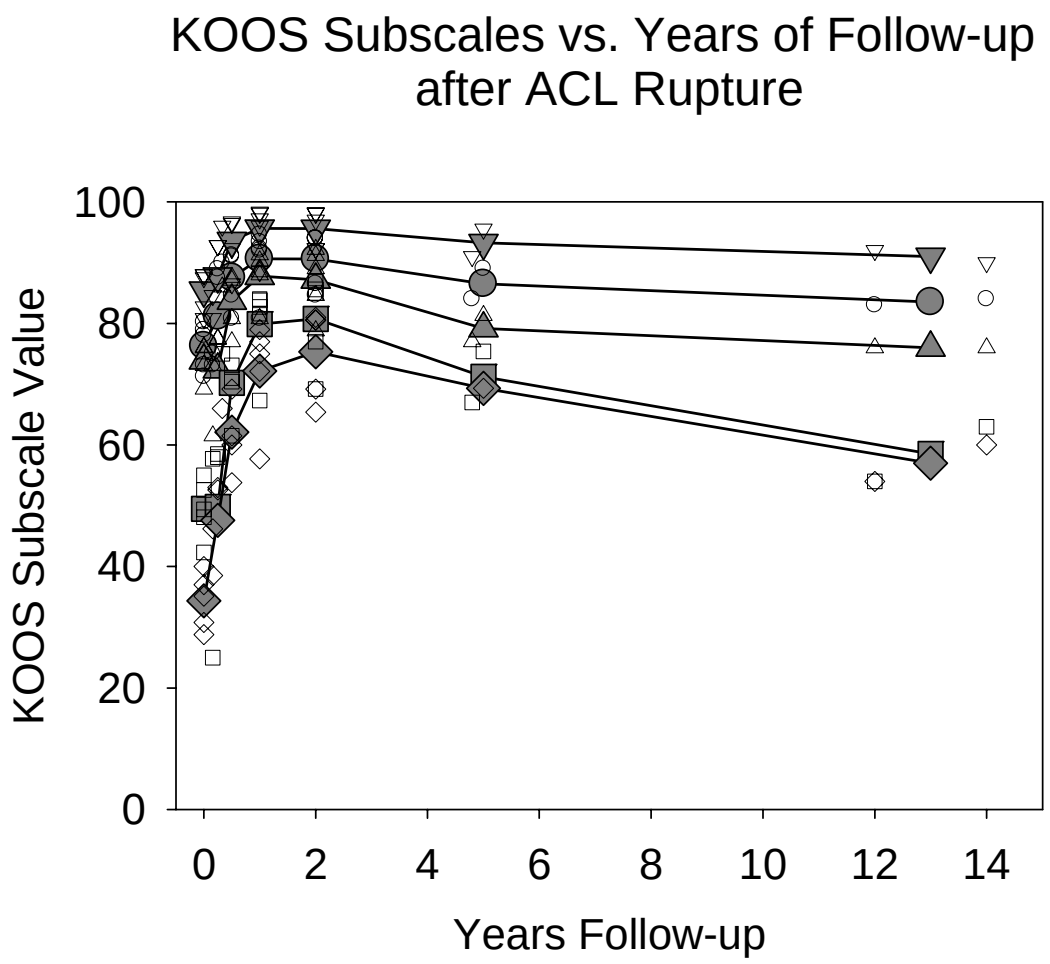

KOOS Subscales vs. Years of Follow-up after ACL Rupture
KOOS Subscale Value
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Years Follow-up

Figure 6

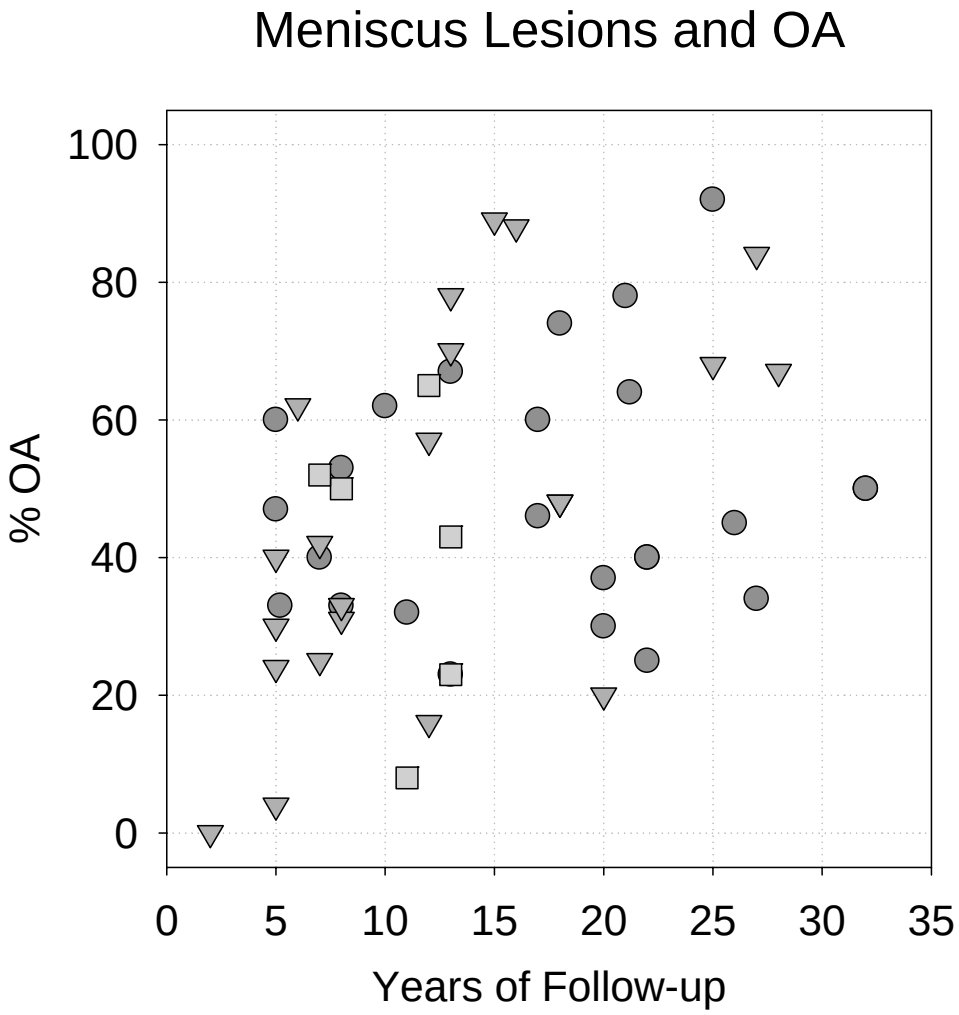

Meniscus Lesions and OA
% OA
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Years of Follow-up

Figure 7

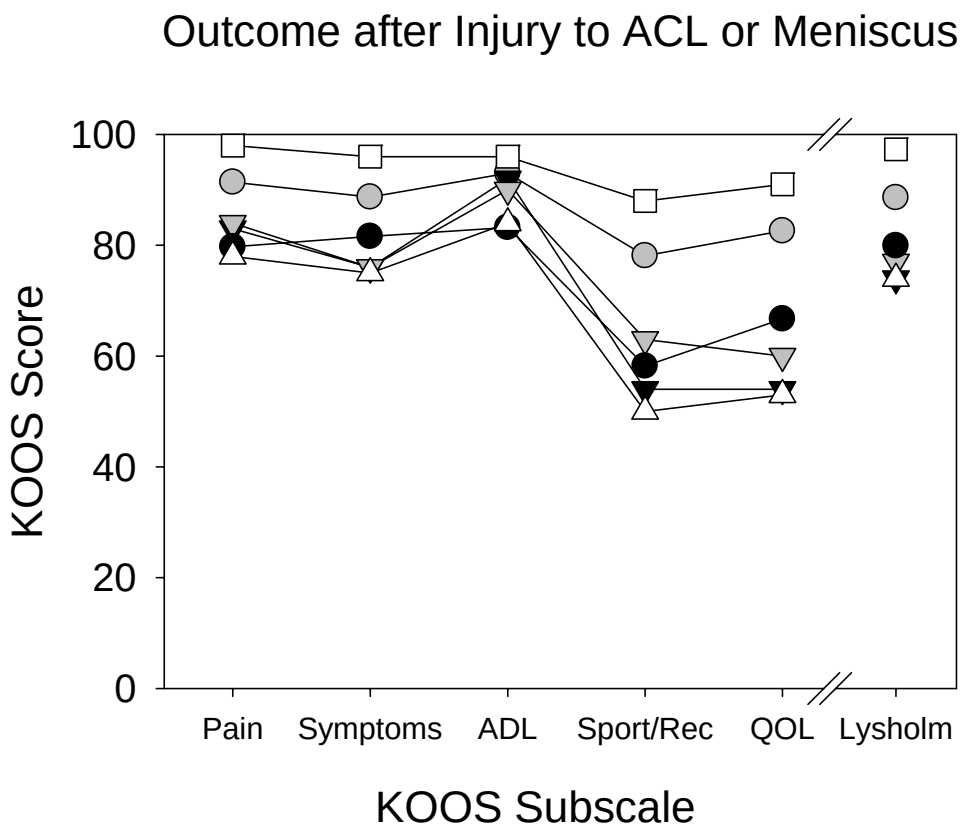

Outcome after Injury to ACL or Meniscus
KOOS Score
100
80
60
40
20
0
Pain
Symptoms
ADL
Sport/Rec
QOL
Lysholm
KOOS Subscale

Figure 8

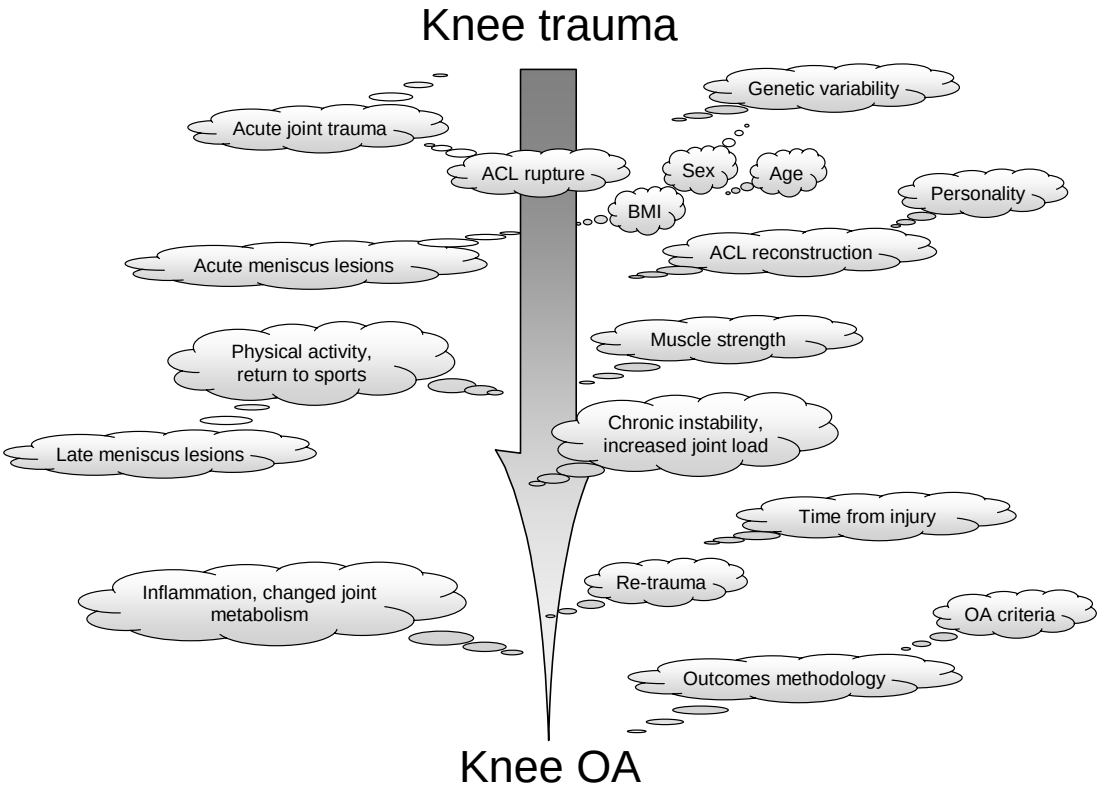
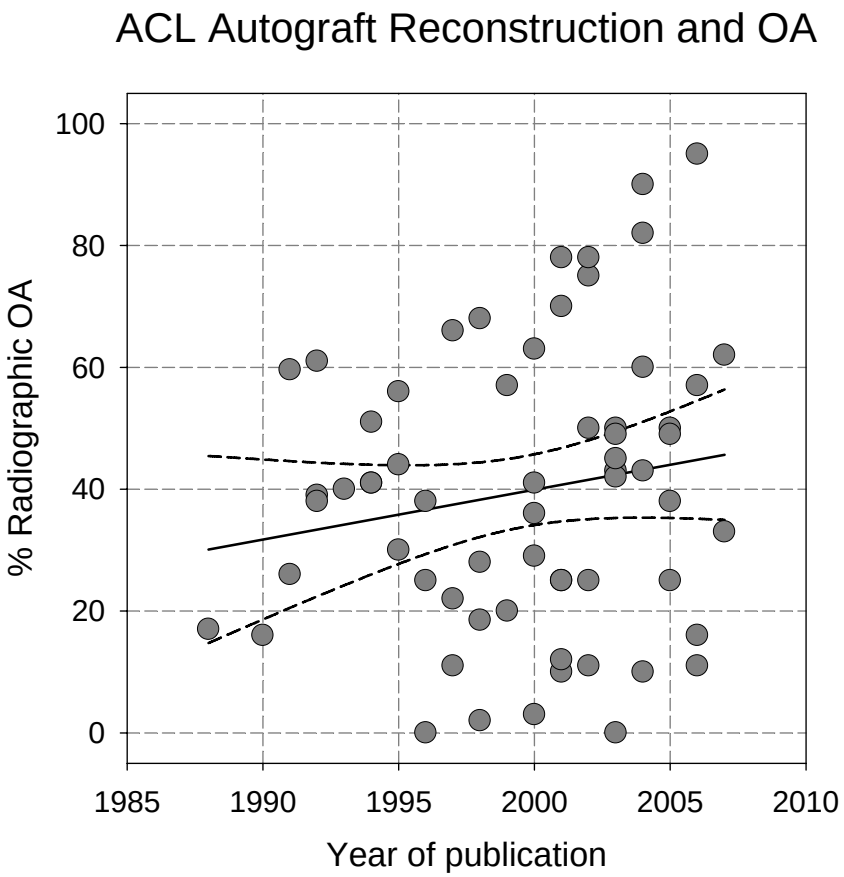

Knee trauma
Genetic variability
Acute joint trauma
ACL rupture
Sex
Age
Personality
BMI
ACL reconstruction
Acute meniscus lesions
Muscle strength
Physical activity,
return to sports
Chronic instability,
increased joint load
Late meniscus lesions
Time from injury
Re-trauma
Inflammation, changed joint
metabolism
OA criteria
Outcomes methodology
Knee OA

Figure 9


ACL Autograft Reconstruction and OA
% Radiographic OA
100
80
60
40
20
0
1985
1990
1995
2000
2005
2010
Year of publication