THE LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE DEVELOPMENT OF RADIOGRAPHIC KNEE OSTEOARTHRITIS

Dr VICTORA L JOHNSON

Doctorate of Philosophy

The University of Sydney

THE LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE DEVELOPMENT OF RADIOGRAPHIC KNEE OSTEOARTHRITIS

V.L. JOHNSON

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Victoria Johnson

ACKNOWLEDGEMENTS

I would like to dedicate my PhD thesis to my beautiful mother, Lee. Your path through life constantly inspires me. Thank you for showing me that strong, hard-working and intelligent woman are valuable and that we can conquer any challenge, overcome any obstacle, and can achieve extraordinary things. There is no glass ceiling because you took me by the hand and showed me the way. I would not be the person I am today without. Thank you for your love, support, encouragement and passion.

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ABSTRACT

The knee is one of the most commonly injured joints with injury to the anterior cruciate ligament (ACL) being strongly associated with an increased risk of knee osteoarthritis (OA). As the risk of ACL injury is highest amongst adolescents who participate in sports the majority of the literature has focused on knee injury amongst this cohort. It is not currently understood whether a similar relationship exists in an elderly population.

This thesis utilised participants from two different cohorts, the first being the Osteoarthritis Initiative (OAI), which is an ongoing 10-year, multi-centered, prospective observational study designed to identify risk factors for the development and progression of knee OA. This cohort was utilized in chapters 3, 5, 6 and 7 to investigate whether elderly individuals with an ACL tear were at an increased risk of radiographic knee OA and to further examine the relationship between the severity of radiographic disease and the extent of injury to the ACL and the surrounding tissues as well as for the presence of knee symptoms. The second cohort was a 15-year prospective, longitudinal, single center study that contained participants who underwent primary reconstruction following ACL rupture. This cohort was utilized in chapter 4 to assess whether an age-related dose-response relationship existed for incident radiographic knee OA following ACL injury.

Overall, knees that had a loss of ACL integrity secondary to age-related degeneration did not have an increased risk of incident radiographic knee OA. However, an ACL injury sustained in an aged knee was associated with an increased risk of radiographic

OA development within the first 5 to 10 years of the initial injury and an increased risk of region specific disease progression secondary to meniscal and subchondral bone pathology. Overall joint damage patterns were similar amongst individuals with either a partial or complete ACL rupture suggesting that joint health carries a similar prognosis regardless of the extent of ACL fiber disruption. Finally, a loss of ACL integrity and radiographic OA severity was also associated with knee disability.

Whilst injuries amongst the younger, active population have been the focus of study for the association of injuries and OA, injury amongst older adults demands significant attention.

PUBLICATIONS

Narrative Literature Reviews

V. L. Johnson, B. M. Giuffre, D. J. Hunter. Osteoarthritis: What does imaging tell us about its etiology? *Seminars in Musculoskeletal Radiology*. 2012; Volume 16(5), pages 410 – 418.

V. L. Johnson, D. J. Hunter. The epidemiology of osteoarthritis. *Clinical Rheumatology*. 2014: Volume 28(1), pages 5 – 16.

Original Publications

V. L. Johnson, C. K. Kwoh, A. Guermazi, F. Roemer, R. M. Boudrea, T. Fujii, M. J. Hannon, D. J. Hunter. Loss of anterior cruciate ligament integrity and the development of radiographic knee osteoarthritis: a sub-study of the osteoarthritis initiative. *Osteoarthritis and Cartilage* 2015; Volume 23, pages 882 – 887.

V.L. Johnson, J Roe, L Salmon, L Pinczewski, D.J. Hunter. Does age influence the risk of incident knee osteoarthritis following traumatic anterior cruciate ligament injury? *American Journal of Sports Medicine* 2016; Volume 44, pages 2399 – 2405.

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. A comparison in knee osteoarthritis joint damage patterns amongst individuals with an intact, complete and

partial anterior cruciate ligament rupture. *International Journal of Rheumatic Disease*. DOI: 10.1111/1756-185X.13003

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. The association between radiographic anterior cruciate ligament tear and joint symptoms: Data from The Osteoarthritis Initiative. Currently under final Editor Review at *International Journal of Rheumatic Disease*

International Conference Presentations

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. "The Difference in the Pattern of Joint Damage in Knee Osteoarthritis in Knees with Partial and Complete ACL Rupture." Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis. Amsterdam, the Netherlands. April 2016.

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. Loss of anterior cruciate ligament integrity and the risk of secondary meniscal injury and bone marrow lesions: Data from The Osteoarthritis Initiative. Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis. Las Vegas, the United States of America. April 2017.

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mucoid degeneration (black arrowhead). C. Another knee with a partial ACL tear exhibits a complex tear of the posterior horn of the lateral meniscus reaching the superior, inferior and posterior surfaces (white arrows). In addition there is superficial cartilage loss at the posterior lateral tibial plateau (filled arrowhead), a finding more commonly seen in those knees with prevalent ACL damage compared to those without. 172

ABBREVIATIONS

ACL	Anterior Cruciate Ligament
BMI	Body Mass Index
BML	Bone Marrow Lesions
DESS	Dual-Echo at Steady-State (DESS)
FINH	Foundation for the National Institutes of Health
FOV	Field Of View
FS	Fat Saturated
GEE	General Estimating Equation
IW	Intermediate-weighted
JSW	Joint Space Width
KLG	Kellgren-Lawrence Grading
KOOS	The Knee Outcomes in Osteoarthritis Survey
MMP	Matrix Metalloproteinases
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OR	Odds Ratio
PA	Postero-anterior
ROA	Radiographic Osteoarthritis
SD	Standard Deviation
SF12	The Medical Outcomes Study Short Form 12
TE	Time to Echo
TR	Time to Recover
WOMAC	The Western Ontario and McMasters Osteoarthritis Index

CHAPTER 1

LITERATURE REVIEW

This chapter includes the following published literature review:

V. L. Johnson, B. M. Giuffre, D. J. Hunter. Osteoarthritis: What does imaging tell us about its etiology? *Seminars in Musculoskeletal Radiology*. 2012; Volume 16(5), pages 410 – 418.

OSTEOARTHRITIS: WHAT DOES IMAGING TELL US ABOUT ITS ETIOLOGY?

Authors: Victoria L Johnson, Bruno M Giuffre, David J Hunter

Abstract

Osteoarthritis (OA) is the most common joint disorder, and a leading cause of disability. Due to an aging population and increasing obesity the incidence of OA is rising. The etiology of OA is multifactorial and complex thus prevention of OA remains challenging. Risk factors can be divided into person-level factors, such as age, sex, obesity, genetics, race/ethnicity and diet, and joint-level factors including injury, malalignment and abnormal loading of the joints. This narrative review provides a brief overview on the person level risk factors and a more in depth analysis of those at the joint level. It is only through an improved understanding of risk factors for disease that we may be able to meaningfully intervene to prevent its occurrence.

Corresponding Author: Victoria L Johnson

Introduction

Osteoarthritis (OA) is the most common joint disorder affecting approximately 15% of the population, 50% of those over 65 years and 85% of those 75 years or older[1]. OA most commonly affects the hip, knee and hand joints. Given its preference for lower extremity joints, OA is the leading cause of lower extremity disability amongst older adults[1]. The risk for disability attributable to knee OA is as great as the risk attributable to cardiovascular disease and greater than that caused by any other medical condition in elderly adults. OA is also the most common reason for a total knee replacement or total hip replacement[1].

As the prevalence of OA is projected to double by the year 2020, due in part to an aging population and an increase in the prevalence of obesity, OA is likely to have a large impact on the health care and public health systems in the future[2]. This narrative review provides a brief overview on the person level risk factors and a more in depth analysis of those at the joint level. It is only through an improved understanding of risk factors for disease that we may be able to meaningfully intervene to prevent its occurrence.

Defining Osteoarthritis

OA can be defined pathologically, radiographically or clinically. Due to the ease of standardization and acquisition, radiography is often used as the standard for defining the presence and severity of OA using the Kellgren and Lawrence grading system[3]. It is more clinically relevant to measure individuals with symptomatic OA as not all persons who have radiographic OA have concomitant symptoms, and not all

individuals who experience joint symptoms demonstrate radiographic OA[4] .

Incidence and Prevalence of OA

Approximately 6.8% of adults aged 26 or older have radiographic hand OA[5] whilst 19% of adults aged 45 or older have radiographic knee OA[6] according to the Framingham Osteoarthritis Study. The Johnston County Osteoarthritis Project approximated that 28% of women aged 45 or older had hip OA[7].

The prevalence estimates of symptomatic OA are lower since its presence is defined by a combination of radiographic OA with pain and stiffness in the joint. The Framingham Osteoarthritis Study found that the prevalence of symptomatic knee OA was 7% of adults aged 45 or older[6] whilst symptomatic hand OA was approximated at 13.4% and 26.2% in men and women, respectively in adults aged 71 years or older[5]. Symptomatic hip OA was present in approximately 10% of the Johnston County cohort[7].

Risk Factors

OA has a multi-factorial etiology such that a different set of risk factors can act together to cause OA to develop in any given individual. Thus, OA can be considered as the phenotypic manifestation of a series of different pathways leading to a common end-stage pathology (Figure 1).

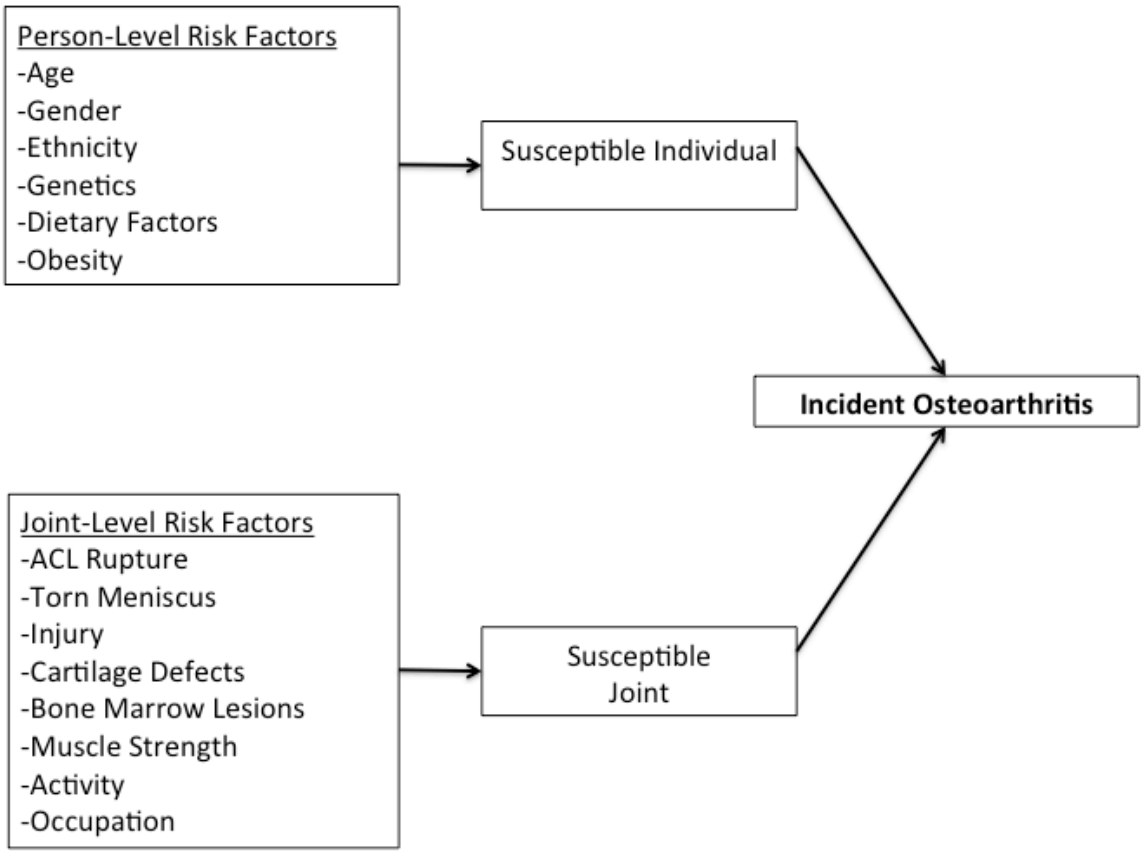

Figure 1: Risk factors that can cause increased susceptibility to OA incidence and progression.

Person-Level Risk Factors

Age

Age is one of the strongest predictors of OA[8]. The exact mechanism/s behind the increased prevalence and incidence of OA with age is poorly understood but is probably a consequence of a combination of biological changes that occur with aging including cellular senescence and exposure to risk factors leading to the joint having a reduced capacity to adjust to biomechanical challenges as a consequence of age related sarcopenia and increased bone turnover.

Gender

The prevalence and incidence of OA is higher in females than males with women more often affected with hand, foot and knee OA than men [9]. In addition, women are more likely to suffer more severe radiographic knee OA than men, particularly following the menopause[9]. Gender disparities may also be caused by differences in bone strength, alignment, ligament laxity, pregnancy and neuromuscular strength.

Racial and Ethnic Disparities

The pattern of joints affected and the prevalence of OA varies amongst racial groups. The National Health and Nutrition Examination Survey 1 suggested higher rates of knee OA in African-American women but not men[10]. Results of the Beijing Osteoarthritis Study showed that the prevalence rate of hip and hand OA is less frequent in Asians than white populations[11] but that Chinese women had significantly higher prevalence of knee OA than Caucasian women (46.6% vs 34.8%) [12]. The factors explaining these differences are poorly understood but likely relate to genetic, environmental, anatomical, and biomechanical features.

Obesity

Obesity is a very important risk factor for OA, particularly in the knee[8]. Being overweight not only antedates the development of disease but also increases the risk of radiographic progression[8]. Men and women with a BMI between 30 and 35kg/m2 have almost 4.8 and 4 times the risk of knee OA than of men and women with a BMI under 25kg/m2 respectively[10]. For every kilogram of increased body weight, the overall force across the knee in single-leg stance increases four-fold[13]. The Framingham Study showed that weight reduction by 5kgs provides a decreased risk for the development of knee OA by 50%[14], confirming that obesity is a modifiable target for prevention of knee OA. Since obesity is increasing in prevalence and is also a risk factor for OA development, it is likely that more individuals will be affected by knee OA in the future.

The relationship between body weight and hip OA is inconsistent and weaker than knee OA[8, 15]. Obesity is also associated with hand OA conferring that obesity may also provide some metabolic and inflammatory effects[16].

Genetics

OA in all of its forms appears to be strongly genetically determined. Genetic factors account for at least 60% of hip and hand OA, with knee OA up to 40%[17]. However, OA is a polygenic disease so the overall effect of each individual susceptibility gene is only moderate. Genome wide association studies have identified the growth differentiation factor 5 gene (GDF5) and the 7p22 chromosome as the main contenders for OA susceptibility. Other signals, such as DIO2, SMAD3 and

ASPN may also be involved in OA susceptibility.

Diet

Continuous exposure to oxidant species contributes to the development of age-related diseases, such as OA, by damaging articular tissues[18]. High vitamin C intake was shown to reduce the progression of radiographic knee OA threefold as well as reducing the risk of developing knee pain[18]. Vitamins D and K are associated with several aspects of bone and articular cartilage metabolism. A diet deficient in vitamins D and K can increase the progression of knee and hip OA whilst an adequate intake of vitamin D might slow disease progression[19, 20]. Fish oil contains the polyunsaturated acid omega-3 and this fatty acid has been found to be chondroprotective and an anti-inflammatory agent in *in vitro* studies[21].

Joint-Level Risk Factors

Occupation

Repetitive joint use has been associated with an increased risk of OA. Studies have found that individuals whose occupations require squatting, kneeling or carrying heavy loads have twice the risk of developing knee OA than occupations that do not require physical activity[22]. Prolonged standing and lifting have also been associated with hip OA[23]. Occupations that require dexterity, particularly repeated use of a pincer grip, have an increased risk of developing OA at the distal interphalangeal and the metacarpophalangeal joints[24].

Exercise and Physical Activity

The issue of repetitive joint use may also be pertinent for physical activity. Multiple population-based studies[25, 26] have found that high levels of physical activity increase the risk of developing knee and hip OA. However, when sporting injuries and joint impact are accounted for there is no evidence to support a deleterious effect of physical activity on normal joints[27]. Conversely, there is an association between developing OA and participating in elite level sport. Elite athletes that participate in repetitive, high intensity and high impact sports (such as running, dancing, tennis, squash and team sports) have an increased risk of developing radiographic hip and knee OA when compared to an age-matched, non-elite cohort[27]. Whether this is solely due to sport participation or as a result of injury is unclear thus when considering an individuals risk of developing OA due to exercise the most important aspects to consider are; the type of sport, its intensity and a history of joint injury.

Internal Joint Risk Factors

Anterior Cruciate Ligament Injury

The anterior cruciate ligament (ACL) provides the main restraint of anterior tibial translation at the knee and as such is the most commonly injured knee ligament, particularly in sports that require pivoting. The incidence of ACL rupture is 81 per 100,000 annually between the ages of 10 and 64 years[28]. For high risk sports, the risk of rupturing the ACL is up to 1000 times higher than the general population[29]. The risk of rupture is higher in adolescents than adults and up to 5 times higher in adolescent women than men[30, 31]. Thus, given that the majority of patients that suffer from an ACL injury are adolescents, ACL injuries may lead to a large number of individuals with early-onset knee OA[29] as individuals who suffer a knee injury have a 5 times increased risk of developing knee OA[32].

An isolated ACL injury isn't common, rather injury of the ACL is associated with injuries to the cartilage, subchondral bone, menisci and other ligaments[29] as shown in Figure 2.

Figure 2a

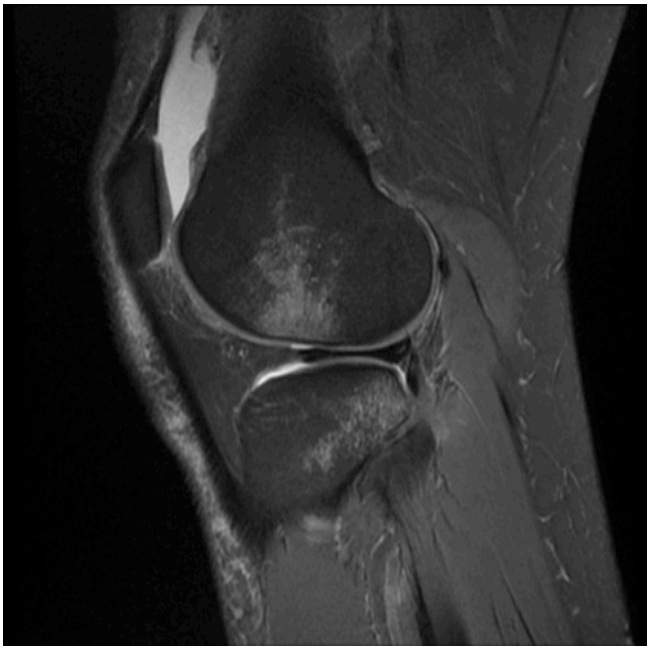

Figure 2b

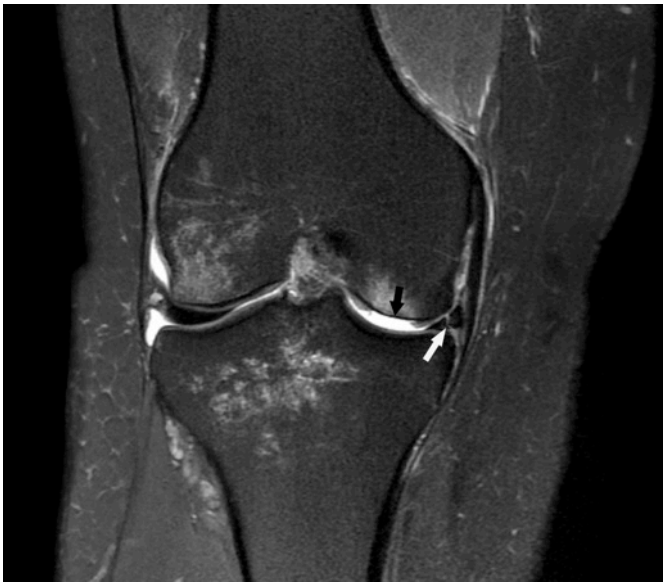

Figure 2: A 46 year old woman with recent acute twisting injury to knee resulting in anterior cruciate ligament tear, as well as tear of medial meniscus and a focal cartilage defect of the medial femoral condyle: (a) Sagittal fat suppressed fast spin echo proton density image of complete tear of anterior cruciate ligament with characteristic impaction bone bruises from translational component of injury (b) Coronal fat suppressed fast spin echo proton density image with vertical tear of the posterior medial meniscus (white arrow) and 10mm full thickness cartilage loss of medial femoral condyle (black arrow).

The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. It has been postulated that the majority of the tissue damage is related to the large forces required to injure the ACL[33]. In addition, intra-articular bleeding commonly occurs with the initial injury, as well as the surgical repair, causing both an acute and sustained release of inflammatory cytokines and proteases from joint tissues[34] which may lead to further damage of the type 2 collagen network.

Changes in the static and dynamic loading of the injured knee are also apparent due to the lack of a functional ACL. There are significant differences in the tibiofemoral motion of ACL-deficient knees with respect to healthy controls[35]. There is increased tibial internal rotation and posterior translation throughout the stance phase of walking altering tibiofemoral loading patterns. This changes the region of cartilage that is in contact during weight bearing causing increased loading of areas that were not conditioned to constant load prior to injury.

Two studies focusing on soccer players found a high prevalence of knee OA in both female[30] and male[36] athletes. Twelve years after an ACL injury 41% and 51% of men and women exhibited radiographic knee OA respectively. None of subjects reported OA in their non-injured contralateral knee. These results are consistent with a review by Lohmander, who suggested that 50% of individuals who suffer a traumatic ACL injury develop OA[29].

Yet despite these studies, a 2008 systematic review concluded that the prevalence of knee OA with an isolated ACL rupture was as low as 13%[37]. Thus, with such a

large range in the prevalence of knee OA attributable to ACL injuries the study methods and outcome measures used to ascertain OA needs to be more consistent across studies.

Studies have also looked at the prevalence of knee OA in subjects that have undergone ACL reconstructive surgery against those that had conservative treatment. Both these treatment groups showed the same prevalence of knee OA[38, 39] leading a Cochrane review to declare that there is insufficient evidence to determine which method of treatment is best for ACL injuries[40]. A study of European handball players found that 22% of those who returned to their sport post-ACL reconstruction would later reinjure their ACL[31]. If long-term joint health is the primary concern this raises questions as to whether returning to sports that involve pivoting is really in the athletes long-term interest with regards to joint health. Consequently it is important to note that whilst surgery may repair the ligament in the short-term it does not prevent the development of knee OA in the long-term[37, 38] nor does it protect the knee from re-injury. This highlights that the major intra-articular changes that occur at the time of injury may confer the risk to later OA development.

Paradoxically, knee OA may also cause injury to the ACL. Amin et al[41] found that among subjects with established radiographic knee OA between 20-35% had an incidental ACL tear (see Figure 3). Established OA may cause degenerative changes within the ACL and thus make it prone to rupture without major trauma. In addition, an ACL tear in established knee OA will accelerate the progression of knee OA[42].

Figure 3a

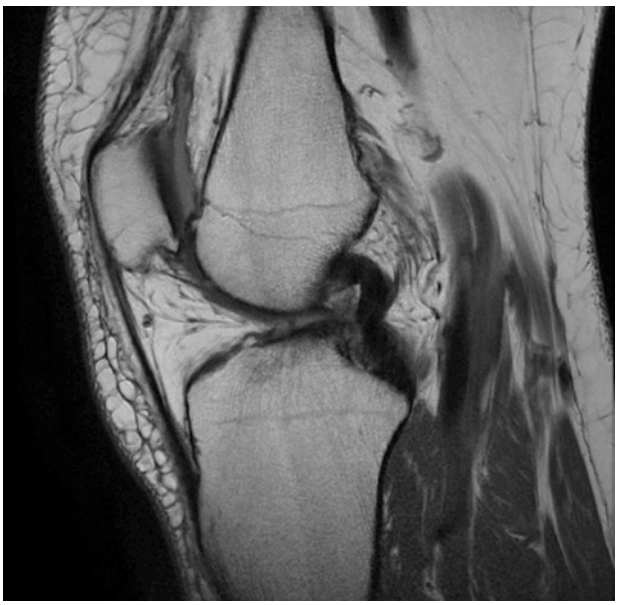

Figure 3b

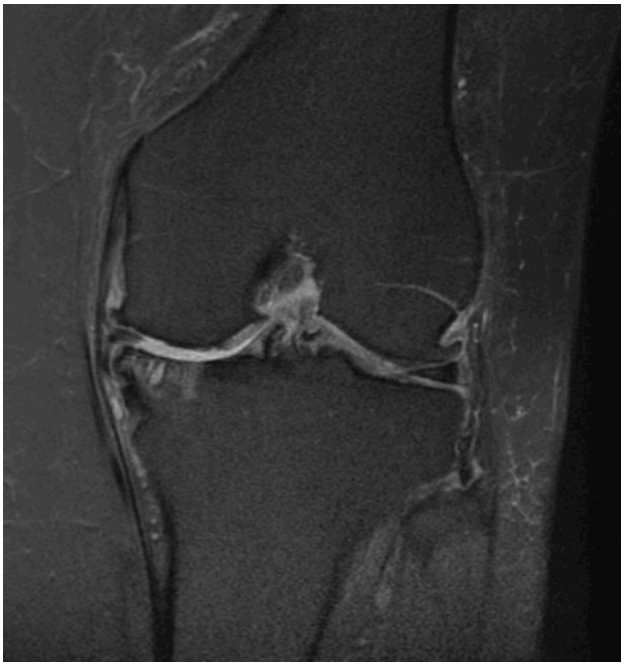

Figure 3: A 65 year old woman with extensive medial compartment osteoarthritis and chronic anterior cruciate ligament tear: (a) Sagittal fast spin echo proton density image with redundant posterior cruciate ligament as a result of anterior cruciate ligament deficiency (b) Coronal fat suppressed fast spin echo proton density image with marked longstanding cartilage loss and secondary tibial subchondral marrow lesion and cyst formation.

Injury to the Meniscus

The meniscus plays a protective role in each of the tibiofemoral compartments, acting as a shock absorber and aiding the distribution of load across the joint surface, thus contributing to joint stability and proprioception.

There are two main meniscal lesions; traumatic and degenerative. Traumatic lesions usually occur as a result of an acute trauma in younger, active individuals, are often symptomatic and have been shown to carry an increased risk of developing knee OA[43]. Degenerative lesions, as shown in Figure 4, often occur in middle aged and elderly individuals with knees that have already been compromised by OA[43].
An analysis of meniscal lesions found that a greater number of tears occur in the medial than the lateral meniscus (37% vs 16%)[44]. Since the medial meniscus is firmly attached to the joint capsule it is more likely to become trapped between the femoral condyle and the tibial plateau under extreme forces. The lateral meniscus is more mobile therefore it is injured less frequently.

Figure 4

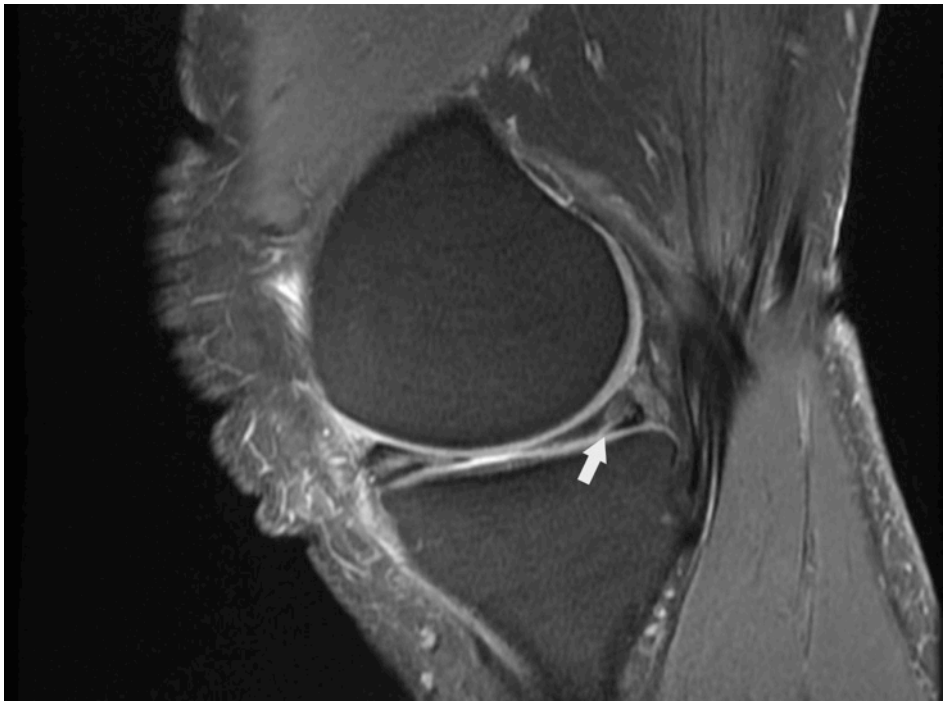

Figure 4: A 74 year old with degenerative horizontal tear of posterior medial meniscus and thinning of articular cartilage: Sagittal fat suppressed fast spin echo proton density image demonstrating a horizontal tear of the posterior medial meniscus (white arrow).

The Framingham Study found that 82% of subjects who displayed radiographic knee OA had meniscal damage with the majority suffering from degenerative lesions[45]. Bhattacharyya et al found that 91% of subjects who had symptomatic knee OA had a meniscal tear[46]. Intra-meniscal signal changes were a frequent finding even when a tear was not present on MRI. These signals may signify the beginnings of meniscal deterioration and thus represent a precursor to a degenerative lesion[47]. The long-term radiographic outcome for those subjects with a degenerative lesion has been found to be worse than those with traumatic lesions[43] including an increased risk for early onset OA[29].

Recent literature has argued as to whether or not damage to the meniscus is a cause or consequence of knee OA[48]. Normally organised menisci are rarely found in patients with knee OA suggesting that there is a strong disorder of the meniscus involved with the development of OA[45, 46]. Middle-aged and elderly subjects who have radiographic meniscal damage are at higher risk of developing knee OA, as evidenced in Figure 5, than in subjects who have normal menisci[49] This suggests that damage to the meniscus antedates radiographic cartilage changes.

Cartilage destruction due to the pathological processes that are active during the early stages of OA could also affect meniscus and ligament integrity as well. Thus knee OA may also cause meniscal lesions and act to further accelerate the disease[50].

Surgery is the most common form of treatment for injuries to the menisci. However, just like ACL reconstructions, surgery might be able to fix the meniscus in the short-term but it cannot prevent the incidence of symptomatic radiographic knee OA,

regardless of whether a total or partial meniscectomy is performed[43, 49]. Meniscal replacement surgeries including the use of allogeneic, xenogeneic and artificial menisci have been tried in younger patients but the transplant survival is variable and long-term results are lacking[29].

Figure 5a

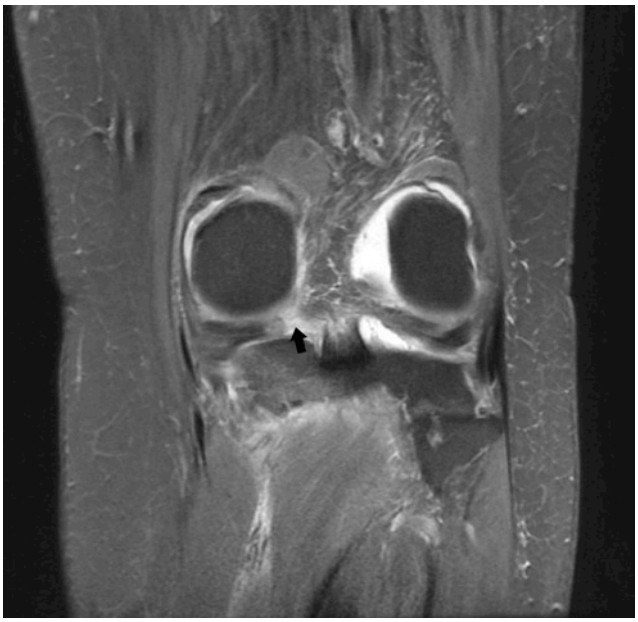

Figure 5b

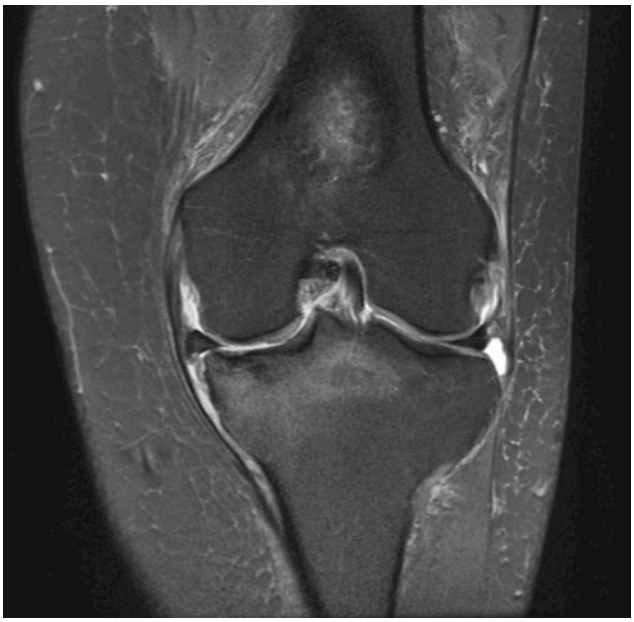

Figure 5c

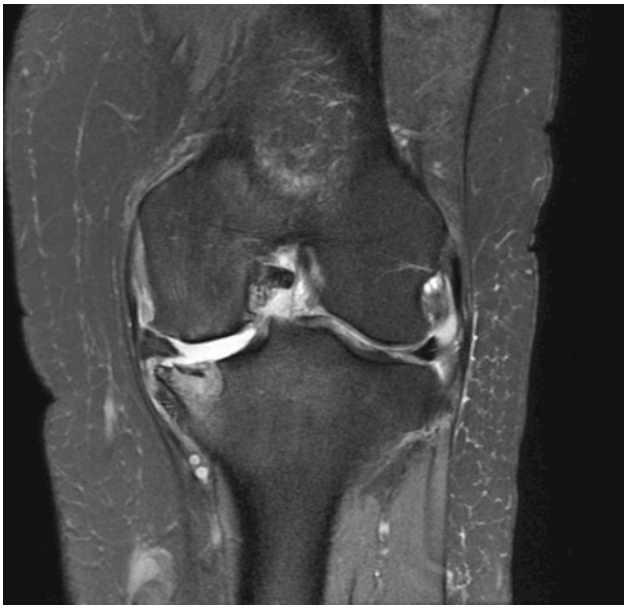

Figure 5: A 70 year old woman who had a minor injury, with a defunctioning medial meniscal root tear and displacement of the body of meniscus. (a) Coronal fat suppressed fast spin echo proton density image with tear of medial meniscal root (b) Coronal fat suppressed fast spin echo proton density image with medially displaced and defunctioned medial meniscus (c) A follow-up study 10 months later demonstrated rapid loss of articular cartilage and a focal subchondral collapse of the tibial plateau. Coronal fat suppressed fast spin echo proton density image with virtual loss of all articular cartilage over femoral and tibial surfaces as well as minor subchondral collapse and bone oedema tibia.

Cartilage

Articular cartilage is both aneural and avascular thus cartilage is unable to produce pain, stiffness, inflammation or any other symptom of OA[51]. OA was once considered a primary disorder of the articular cartilage but now it is widely appreciated that multiple structures are involved and affected in the development of OA.

Cartilage pathology in OA is a balance between synthesis and degradation of the articular cartilage matrix. Excessive matrix degradation increasingly overwhelms matrix synthesis due to an excess of inflammatory, catabolic signals, matrix metalloproteinases (MMPs) and aggrecanases which act to further degrade the cartilage matrix[51, 52].

Adult chondrocytes rarely divide thus they can accumulate reactive oxidative species which can cause altered cell viability and chondrocyte death. Recent evidence suggests that during the development of OA there is increased cell proliferation and an up regulation of synthetic activity resulting in clusters of chondrocytes[51, 52]. Despite this, these cells are not able to maintain the integrity of the cartilage matrix, mainly due to their inability to respond to growth factors, and thus further contribute to the increased matrix degradation and the destruction of type II collagen[51, 52]. These changes are also accompanied by cartilage surface fibrillation and the production of fibrocartilage[52].

It has previously been suggested that cartilage thinning posed an increase risk for OA and may in fact represent the initial pathology of OA[53]. However, recent studies

suggest that early osteoarthritic cartilage may be thicker and swollen with water due to disruption of the collagen network along with altered proteoglycans. It was proposed that focal areas of denuded cartilage and increased cartilage thickness may be part of the initial evolution of the disease and that cartilage defects may occur in early knee OA and precede cartilage volume loss[54, 55]. In patients with symptomatic OA, progression of cartilage defects over 30 months was found in 46% and 22% for the medial and lateral tibiofemoral compartments respectively. Furthermore, cartilage defects are also associated with bone expansion, bone marrow lesions (BML), meniscal injuries and ACL rupture suggesting that they have multiple causes[55]. MRI is able to capture these initial structural changes in the earliest phases of the disease whilst changes such as joint space narrowing as detected by radiographs emerge at a much later stage[55].

Subchondral Bone

Bone cells are more able to self-repair and modify their surrounding extracellular matrix than articular cartilage[51, 52]. Subchondral bone undergoes adaptations during the development of OA including increase in subchondral plate thickness, sclerosis, joint space narrowing, reduced matrix mineralisation, increased cancellous bone volume, formation of osteophytes at the joint margins, development of bone cysts and advancement of the tidemark associated with vascular invasion of the calcified cartilage. These changes may cause alterations in the adjacent joint surfaces, which in turn will change the joint congruity and hence progress the disease[52, 56].

It is the adaptive capacity of bone that underlies the more rapid appearance of detectable skeletal changes, especially after joint injuries or with altered mechanics.

The presence of BML correlates with the severity of pain as well as the areas of greatest cartilage loss[52, 56] (see Figure 6). BML were present in 77.5% of subjects who experienced painful knees compared with only 30% of subjects who reported no knee pain[56]. Furthermore, BML have been found to be compartment-specific for cartilage progression. Subjects who were varus in alignment developed medial lesions whilst those who were valgus developed lateral lesions. In terms of bone abnormalities, BML is the only effective risk factor for predicting knee OA progression[56].

Figure 6a

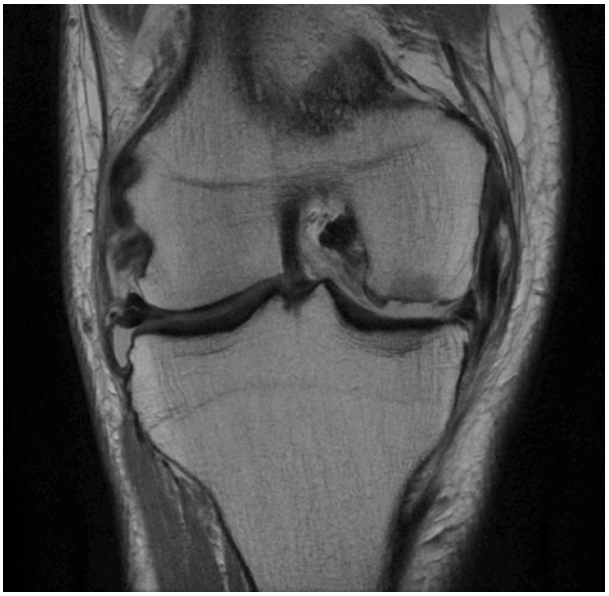

Figure 6b

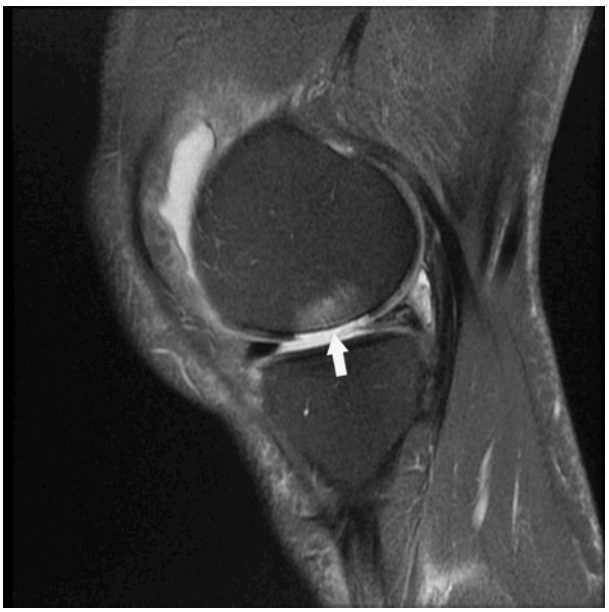

Figure 6: A 70 year old man with an injury to knee resulting in focal cartilage loss: (a) Coronal fast spin echo proton density image with focal defect (b) Sagittal fat suppressed fast spin echo proton density image demonstrating focal cartilage defect (white arrow) with underlying bone marrow lesion and degenerative changes in posterior medial meniscus.

Recent studies[57, 58] in asymptomatic populations discovered that the development of new BML in knees that contained no BML at baseline were associated with the progression of tibiofemoral cartilage defects and loss of cartilage volume reflecting early cartilage pathology. This suggests that not only can BML propagate OA progression but also may play an important role in the pathogenesis of knee OA.

Synovitis and Effusion

Synovitis and effusion are frequently present in OA and are directly responsible for several clinical symptoms and reflect the structural progression of the disease[53] (see Figure 7).

Synovial inflammation is focused in areas adjacent to damaged cartilage and bone and can cause the release of proteinases, inflammatory cytokines, MMPs and aggrecanase[53] that further accelerates the degradation of cartilage. The releases of these inflammatory mediators, as well as the formation of osteophytes may act to irritate sensory nerve endings within the synovium causing pain. MRI analysis of subjects with knee OA showed that synovial thickening was greater amongst subjects who experienced knee pain than in asymptomatic subjects[59].

The clinical symptoms of inflammation along with the presence of histological inflammation in synovial tissue and cartilage lesions at the border of inflamed synovium are strong indicators that synovitis plays a pivotal role in the development of OA. Synovial inflammation also perpetuates disease progression as Roemer et al[60] reported that individuals who displayed moderate to severe baseline synovitis had an increased risk of rapid cartilage loss.

Figure 7a

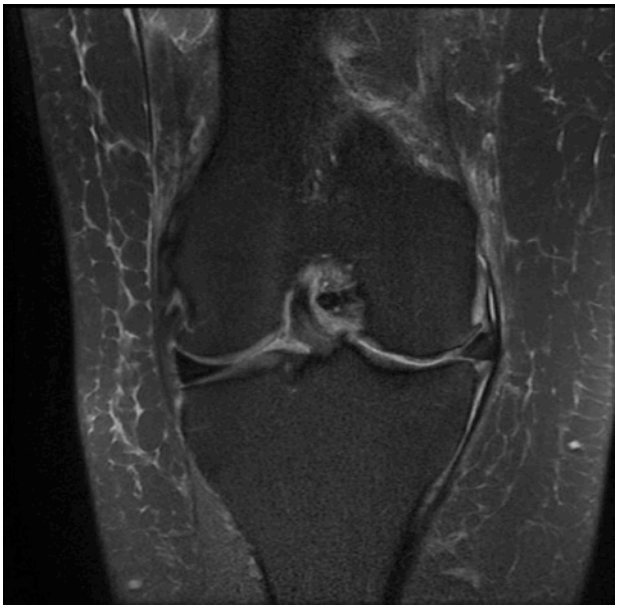

Figure 7b

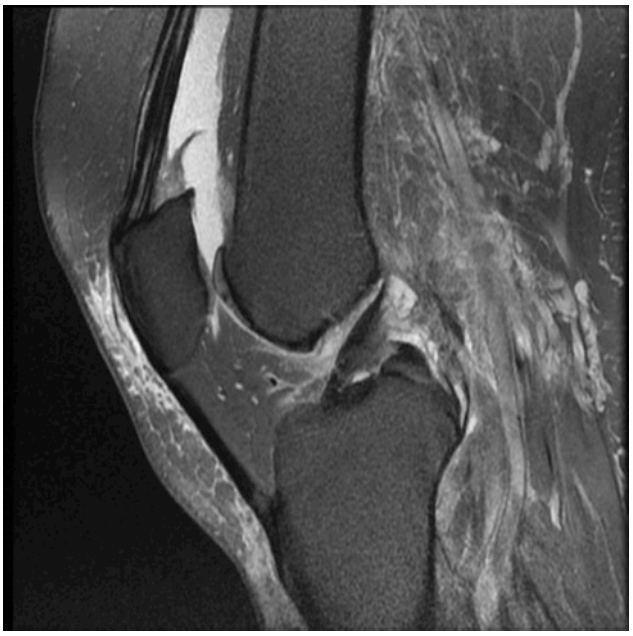

Figure 7: A 65 year old man with longstanding known osteoarthritis of knee and an episode of Synovitis: (a) Coronal fat suppressed fast spin echo proton density image with moderate cartilage loss medial compartment as well as degeneration of medical meniscus. (b) Sagittal fat suppressed fast spin echo proton density image with prominent cartilage loss patellofemoral joint and large suprapatellar effusion.

Mechanical Factors

Quadriceps Strength

Quadriceps femoris is the primary anti-gravity muscle of the lower limb and serves to decelerate the lower limb during ambulation as well as to stabilise the knee. Quadriceps weakness is common amongst OA patients. Baseline knee extensor strength was reduced in women with no knee radiographic changes at the initial examination but developed knee OA 30 months later[61]. This was confirmed by Baker et al[62] who found that subjects with asymptomatic patellofemoral and tibiofemoral radiographic knee OA had reduced quadriceps strength when compared to subjects who did not have OA.

Additionally, quadriceps weakness may also increase the risk of structural damage. For every 5kg increase in extensor strength Slemenda et al, found an associated 20% and 29% reduction in the odds of developing radiographic knee OA and symptomatic knee OA respectively[61].

Alignment

A shift from neutral will alter load distribution across the knee thus malalignment may contribute to abnormal mechanical forces. Knee malalignment is one of the strongest predictors of knee OA progression. A prospective cohort study showed that abnormal alignment was strongly associated with increased structural degradation in the compartment that was under greatest compressive stress[63]. Medial progression of knee OA was four times more likely in individuals with varus alignment, whilst lateral progression was five times more likely in individuals with valgus alignment[64]. BML as well as rapid cartilage loss displayed on MRI have also been

associated with knee malalignment[65]. It is important to note that no study as yet has documented the slowing of disease progression when alignment is corrected.

The association between incident knee OA and malalignment is less apparent. The Rotterdam Study found OR of 2.06 and 1.54 of developing radiographic knee OA in individuals with varus and valgus knee alignment respectively[66]. These results were not supported by the Framingham Study, which found no association between knee joint alignment and an increased risk of incident radiographic knee OA[67].

Summary

As the prevalence of OA in the population continues to rise so does the substantial burden that is placed on the health care system. The etiology of OA is multifactorial and complex thus prevention of OA remains challenging. Risk factors for developing OA are different for each joint. The use of advanced imaging, the measurement of systemic and local biomarkers, combined with the improved methods of measuring symptoms will ultimately help lead to the development of disease-modifying pharmaceuticals and improved non-pharmacologic treatments of OA.

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CHAPTER 2

INTRODUCTION TO ANTERIOR CRUCIATE LIGAMENT INJURIES AMONGST THE ELDERLY

The following chapter contains Methods Tables previously published in the following peer-reviewed article

Peterfy CG, Schneider E, Nevitt M et al. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008:16;1433-1441

Loss of ACL Integrity in the Elderly

There is a well-established relationship between traumatic rupture of the ACL and the subsequent development of knee OA, however it has been postulated that tearing of the ACL might also be a consequence of aging and OA disease progression.

Histological examination of the ACL amongst elderly individuals has revealed that degenerated ACLs exist within knees in the absence of any cartilage degeneration and that the rate of ACL rupture within these knees was as high as 10%[1] suggesting that the initiation of ACL degeneration may either occur before or progress independently of cartilage degeneration.

It was thought that changes in cell organization, reduced cellular recruitment and proliferation by progenitor cells and myofibroblasts as well as an increase in perivascular cell aggregates and matrix metalloproteinase (MMP)-1, -3 and -13 expression, contribute to age-related ACL degeneration in addition to histological alterations such as cystic changes, disorientation of collagen fibres and mucoid degeneration. All of these changes were highly prevalent in the ACL of knees with severe OA even in the absence of previous injury to the ACL [2]. Furthermore, mucoid degeneration severity was found to increase linearly with the onset and progression of cartilage degeneration [2, 3]. Thus, chondroid metaplasia, collagen fibre disorganization and mucoid degeneration of the ACL extra-cellular matrix may co-exist within the context of knee OA and can even occur in individuals without a history of knee trauma[3] ultimately suggesting that disruption of the ACL may signify degenerative failure of the ligament, as opposed to injury.

Additionally, ACL fiber degeneration was closely correlated with progressive cartilage destruction suggesting that intra-articular inflammatory changes either trigger or act to accelerate ACL degeneration[2, 3]. Thus, it has been postulated that chronic intra-articular inflammation may represent a possible mechanism for ACL degeneration in the absence of injury, as knees with cartilage damage have been found to produce significantly higher inflammation scores than those knees without similar radiographic cartilage damage.

As knee trauma represents one of the primary causes of knee OA, when combined with altered ligament morphology due to the natural ageing process theoretically this will place an aged, injured knee at an increased risk of incident radiographic knee OA development earlier than an adolescent who injures their ACL. However, this relationship between age-related degenerative ligamentous changes and subsequent increased risk in ligament rupture or tear causing a significant increased risk of incident knee OA has yet to be established.

One thing that needs to be taken into consideration is the nature of the injury. Posttraumatic knee OA has been widely researched due to its large and increasing prevalence on the sporting field. It has been propositioned that the overriding cause for the increased risk of knee OA later in life is due to the high impact forces applied to the knee at the time of injury, conferring significant injury not only to the ACL but also to surrounding tissues, particularly the meniscus and subchondral bone. In contrast, the suggested cause of ACL injury amongst the elderly is said to be due to age-related ligament degeneration. Ligament rupture or tear would thus only require small forces, meaning that surrounding joint tissues would most likely be spared from

injury. Thus without additional tissue changes, is the risk of OA still likely to be as high in the elderly as it is in young adolescents?

Amin et al[4] examined 265 participants with symptomatic knee OA and established that at baseline 19% of participants had a complete ACL tear. After adjusting for age, body mass index, gender and baseline cartilage scores it was found that a complete rupture of the ACL increased an individual's risk for medial tibiofemoral cartilage loss. However, when the results were adjusted for presence of medial meniscal tears, the increased risk in medial compartment cartilage loss was no longer significant. Thus, an incidental complete ACL rupture and concomitant knee OA did not confer an increased risk of cartilage degeneration and loss above what is facilitated by meniscal pathology. Additionally, Driban et al[5] also felt that a vicious cycle could be created where accelerated knee OA leads to an injury, which subsequently leads to another phase of accelerated knee OA.

Interestingly it was also noted that some participants who had a complete ACL tear had no recollection of a significant knee injury, again suggesting that a complete ACL tear in an elderly population may result from different mechanisms than the acute ACL tear in younger persons.

Only one study to date has looked at age at the time of ACL injury as an independent risk factor for developing knee OA. A retrospective, cross-sectional study by Roos et al[6] investigated potential differences in the incidence and progression of post-traumatic knee OA in mature aged and adolescent athletes. They found that athletes, regardless of age, who injured their ACL playing sport, developed incident

radiographic knee OA, on average about 10 years after the initial trauma. If this ACL injury was combined with concomitant meniscal tears, then the time to radiographic incident OA was shortened to 5 years post the initial injury. Further to this they observed increased radiological signs of cartilage deterioration and worsening of knee symptoms with increasing time after the onset of symptoms and injury.

The BOKS study[7] evaluated the relationship between established knee OA and ACL rupture and found that in 360 subjects with knee pain and radiographic OA at baseline, 22.8% were found to have a complete ACL tear detected by MRI. Furthermore, it was found that more severe radiographic OA existed in participants with a complete rather than partial ACL tear based on Kellegren-Lawrence (KL) grading as well as a higher pain score. However, due to the cross-sectional nature of the study, the investigators could not be sure whether the ACL ruptures pre-dated the onset of OA or whether it occurred during established OA. Thus, ACL rupture could have either instigated disease incidence or be a by-product of disease progression. Similar to the study by Amin et al[4], only half of participants that were found to be ACL-deficient recalled a suffering a significant knee injury.

Regardless of the mechanism of injury, ACL deficient knees are unstable due to changes in knee static and dynamic loading. With respect to healthy control knees, ACL-deficient knees produce significant differences in tibiofemoral motion [8] including an increase in internal rotation and posterior translation of the tibia throughout the stance phase of gait. This ultimately serves to alter the weight-bearing tibiofemoral-loading patterns throughout the gait cycle such that a new, previously unloaded region of cartilage that was not conditioned to constant load prior to injury,

will now be in contact during stance phase. These translational shear forces on previously unloaded cartilage has been speculated as a risk factor for accelerated cartilage degeneration[9]. Finally, ACL deficient knees have frequently been associated with quadriceps femoris muscle dysfunction and thus may play a role in the development and progression of OA[10].

Conversely, several investigations have also demonstrated an association between tearing of the ACL and the presence of meniscal pathology[11]. While any injury to the knee could result in simultaneous injury to the ACL and meniscus, some studies have demonstrated that ACL tears themselves might cause secondary meniscal injury[12], which in turn, might contribute to cartilage loss, thus further demonstrating why the etiology of an ACL tear in the absence of significant trauma deserves further investigation.

Thesis Hypothesis and Aims

The purpose of this thesis was to identify whether injury to the ACL amongst an elderly cohort confers the same risk of OA radiographic incidence as their adolescent counterparts.

To date the primary focus of the literature has been on traumatic ACL injury in adolescents and whether these particular individuals go on to develop radiographic and/or symptomatic knee OA later in life. However the nuances of injury to the ACL have yet to be teased out. For example, whether partial tearing of an ACL produces the same structural knee damage as a complete ligament rupture or whether the age at which an individual sustains a knee injury influences the long-term risk of OA. At the present time there has been little investigation into whether an incidental ACL tear in individuals with established knee OA alters the pattern of synovial joint damage thus the etiology and significance of an incidental ACL tear identified in individuals with already established knee OA also remains unclear. The final chapter provides insight into the physical toll of knee OA and ACL injuries as it aims to answer the question of whether individuals with a history of ACL injury are at increased risk of knee pain, stiffness and reduced functionality and whether particular patient reported symptoms are associated with radiographic severity.

The importance of answering these fundamental questions is underscored by the large economic and physical burden of knee OA. In 2007, it was found that 7.8% of Australians suffered from knee OA, two-thirds of whom were aged under 65 years and that OA is the 3rd largest cause of overall morbidity in developed countries [13].

ACL injuries have an annual incidence of at least 81 per 100,000 people aged between 10 and 64 years[14]. The risk of ACL rupture is even greater amongst individuals who engage in high-risk sports such as volleyball and football with the risk of rupture being 1000 times greater than the general population[15]. The reason why the epidemiology of knee injuries is important lies in the fact that individuals who suffer a knee injury have a 5 times increased risk of developing knee OA as early as 10 years after the initial injury[16].

Currently therapeutic interventions for knee OA are palliative and consist primarily of lifestyle modifications, analgesia and surgical intervention for end-stage joint disease. In the absence of disease-modifying pharmacologic agents such as those used for the traditional inflammatory arthropathies we need to instead focus on the modifiable risk factors, namely obesity, alignment and injury prevention, to decrease disease incidence, progression and symptoms. If a potential relationship between the loss of ACL integrity and the pattern of radiographic joint damage could be established then this would identify a cohort who is at an increased risk of joint instability, disability and potentially joint failure in a truncated time period.

Thus the overall aims of this thesis were:

- To provide a more comprehensive overview of injury to the ACL by investigating the radiographic features of ACL injury amongst an elderly cohort with established knee OA
- To compare the risk of incident radiographic knee OA following ACL injury between elderly and adolescent cohorts

Thesis Methods

The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational cohort study which was designed to assess the risk factors for and the natural history of knee OA incidence and progression.

With this in mind, the scientific objectives of the OAI were:

- *To develop an ethnically diverse cohort of women and men aged 45 to 79 suitable for studying the natural history of, and risk factors for, the onset and progression of knee OA.*
- *To determine the validity of radiographic, magnetic resonance imaging, biochemical and genetic measurements as biomarkers and potential surrogate endpoints for knee OA*[17].”

Recruitment time: 2004 – 2005

Follow-up Time: 2005 – on-going

Study Population: 4796 subjects are enrolled

OAI Aims and Objectives

The OAI aims to create a public archive of biological samples, knee MRIs and knee radiographs collected longitudinally from a clinically characterized population of individuals. This study was comprised of two specific subgroups;

1. Progression Subcohort: Individuals with clinically significant knee OA who were at risk of disease progression
2. Incidence Subcohort: Individuals who were at high risk of initiation of clinically significant knee OA.

As of 2016, 4796 women and men have been recruited and enrolled at four clinical centers. Each individual underwent an initial assessment including an eligibility assessment conducted by telephone, a screening clinic visit as well as an enrollment clinic visit. Follow up consisted of four annual follow- up visits.

At baseline and at each of the annual follow-up visits, knee MRI and radiographs as well as biochemical and genetic disease markers such as blood and urine samples were collected. Each of the study's clinical centers were equipped with a Siemens Trio 3.0 Tesla MRI scanner for knee imaging as well as a standard radiology facility to obtain plain joint x-rays.

Additionally, questionnaires and clinical examination were performed at baseline and each of the annual follow-up visits in order to assess each individual's joint status and to collect data on the risk factors for disease progression and the incidence of knee OA.

Clinical assessments of the study individuals included:

- Questionnaires were used to assess and score an individual's knee pain, stiffness, ache and physical disability. Furthermore, these questionnaires were also used to quantify an individual's use of medications to manage their joint pain.
    - The Western Ontario and McMasters Osteoarthritis Index (WOMAC),
    - The Knee Outcomes in Osteoarthritis Survey (KOOS)
    - The Medical Outcomes Study Short Form 12 (SF 12)
- Clinical knee examination for swelling, tenderness and range of motion, joint-line pain and whether arthritis was evident in other joints
    - Examination of upper leg muscle strength
    - Walking endurance.
- Knee OA risk factors for the initiation and progression of disease
    - Evaluating OA in other joints
    - History of knee injury and knee surgery
    - Abnormal biomechanical stresses on the knees due to a knee alignment abnormality
    - Obesity
    - Heavy physical activities
    - Nutritional factors and use of certain medications, such as bone antiresorptive agents.

Individuals were followed for four years to assess for any changes in the clinical status of the knee including onset or worsening of symptoms and disabilities, onset or

worsening of knee structural abnormalities, radiological changes and finally for changes in the biochemical markers of knee OA.

OAI Study Population

As stated earlier, the OAI recruited two specific sub-cohorts – a progression and an incident cohort.

The Progression sub-cohort was defined as containing individuals with symptomatic knee OA from baseline and were assessed annually for changes in markers consistent with worsening disease.

The Incident sub-cohort was defined as containing individuals without symptomatic knee OA at baseline, but was identified to have specific characteristics that uniquely placed them at an increased risk of developing incident, symptomatic knee OA.

A reference or "non-exposed" group was also included in this study. This compromised of 100 – 200 participants who did not have any of the eligibility risk factors, or radiographic findings of knee OA at baseline.

Overall Inclusion Criteria

- Male or female
- Aged 45 – 79 years
- All ethnic groups were eligible for this study

Incidence Sub-Cohort

As stated earlier, the individuals in the Incidence sub-cohort did not have symptomatic knee OA in either knee at baseline. However, each of these individuals displayed features that placed them at increased risk for later developing symptomatic knee OA. Incident symptomatic knee OA was defined as *"…the first occurrence during the study of frequent knee symptoms and definite tibiofemoral osteophytes in the same knee* [17]."

The inclusion criterion to define an individual as "high risk" was selected from known or presumed incident knee OA risk factors that could be easily assessed over the telephone (during the eligibility assessment). These risk factors, as well as the suitable combination of characteristics in each age and gender subgroup, were selected after analyses of previous data sets that focused primarily on an outcome of symptomatic knee OA.

Eight screening risk factors were used in defining eligibility for the incidence sub-cohort. Participants were included in the cohort if they had any of these risk factors including;

- Frequency of knee symptoms in the past 12 months
    - "Knee symptoms during the past 12 months" was defined using three separate definitions, including;
        - Frequent knee symptoms
        - Frequent use of medications to treat knee symptoms (defined as using medication on most days of the week)
        - Infrequent knee symptoms defined as "pain, aching, stiffness in or around the knee" at any time in the past 12 months but <u>not</u> on most days for at least one month
- Overweight
    - Using gender and age-specific cut points for weight
- Knee injury
    - Defined as a history of knee injury causing difficulty walking for at least a week
- Knee surgery

    - Defined as a history of any knee surgery, including meniscal and ligamentous repairs and unilateral total knee replacement for OA
- Family history
    - Defined as a total knee replacement for OA in a biological parent or sibling
- The presence of Heberden's nodes
- Age (70-79 years)
- Repetitive knee bending
    - Frequent climbing, stooping, bending, lifting, squatting or kneeling

Progression Sub-Cohort

The Progression sub-cohort consisted of individuals with symptomatic tibiofemoral knee OA at baseline. Symptomatic tibiofemoral knee OA was defined as having both of the following in at least one knee at baseline:

- *"Frequent knee symptoms in the past 12 months defined as "pain, aching or stiffness in or around the knee of most days" for at least one month during the past 12 months*
- *Radiographic tibiofemoral knee OA, defined as tibiofemoral osteophytes (OARSI atlas grades 1-3), equivalent to Kellgren and Lawrence (KL) grades of greater than or equal to 2 on the fixed flexion radiograph* [17]."

Exclusion Criteria

The following applied to the entire OAI cohort:

- Rheumatoid arthritis or inflammatory arthritis

- Severe joint space narrowing (OARSI grade 3, or bone-on-bone) in both knees on the baseline fixed flexion knee radiograph
- Unilateral TKR and severe joint space narrowing in the other knee
- Any contra-indications for MRI scanning
- Positive pregnancy test
- Unable to provide blood sample for any reason (e.g. dialysis)
- Use of ambulatory aids other than a single straight cane

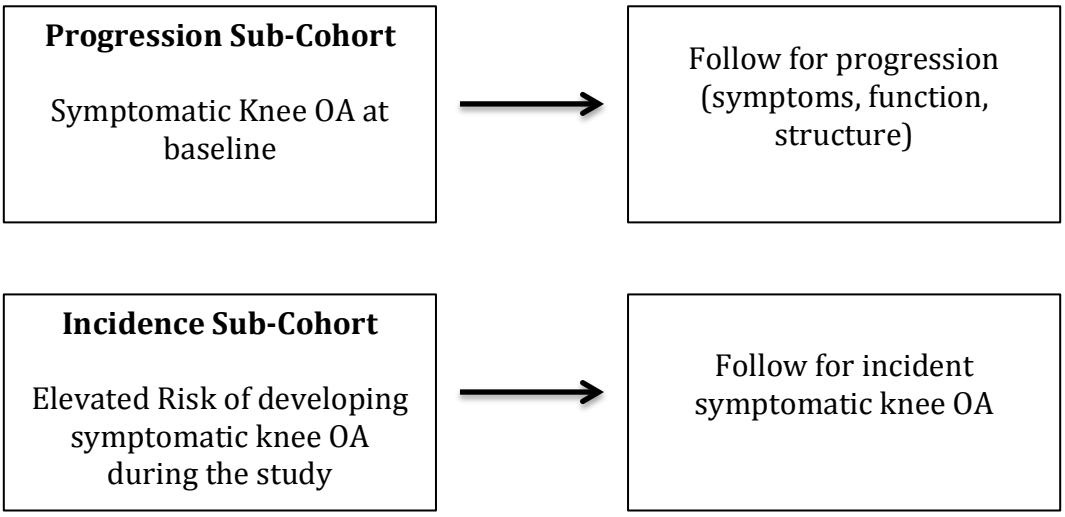

Figure 1: Overview of the OAI Cohort Design

Data Collection and Assessment of Clinical Variables

A core set of outcome measurements, both clinical and imaging, were collected at baseline and at each of the annual follow-up visits. Selection of these measures was guided by the core measures for OA clinical trials as recommended by the Osteoarthritis Research Society. Only the clinical variables that formed the focus of this thesis are outlined below.

Recruitment and Enrollment

The OAI recruitment centers were located at

- Brown University in Rhode Island,
- Ohio State University in Columbus, Ohio,
- University of Maryland/Johns Hopkins University joint center in Baltimore, Maryland,
- The University of Pittsburg in Pennsylvania.

Recruitment and enrollment of participants at baseline involved four stages:

1. Initial contact
    a. Designed to reach individuals within the intended target population through focused mailings, including identified clinical populations with OA, advertisement in local newspapers and a website about knee pain and OA.
2. Initial Eligibility Interview
    a. This was conducted by telephone to determine if each of the interested individuals qualified for the study.
3. Screening Clinic Visit

a. This was organized for all individuals who were deemed eligible following their telephone interview. At this visit additional eligibility assessments were performed

4. Baseline Clinic Visit
    a. For those individuals who were still eligible, all the baseline data including MRI, radiographs and biochemical and genetic markers was recorded at this visit

Knee Examination

A standardized physical examination of the knee was performed at baseline (enrollment visit) and at the follow-up visits on all participants. The examination was performed on both knees and included the following components:

- Visual assessment of knee alignment,
- Anserine bursa tenderness,
- Patellar quadriceps tendonitis/tenderness,
- Crepitus,
- Knee flexion range of motion,
- Presence of flexion contracture,
- Presence of knee effusions,
- Tibiofemoral joint line tenderness,
- Patellar tenderness.

The objectives of the exam were to characterize possible sources of knee pain, assess the severity of selected OA-related knee impairments, to identify findings that may

correlate with abnormalities detected by MRI and to evaluate the prognostic value of standard exam findings.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC questionnaire utilizes a 5-point Likert scale to assess an individual's knee pain, stiffness and knee-related physical disability within the past 7 days[18].

Knee Outcomes in Osteoarthritis Survey (KOOS).

The KOOS questionnaire was specifically designed to include both younger and middle aged subjects with a history of knee injury or post- injury arthritis[19].

Magnetic Resonance Imaging

The MRI protocol aimed to provide a thorough clinical and research evaluation of the tibiofemoral and patellofemoral joints of both knees, making sure to include as many articular structures and features believed to be relevant to knee OA as possible. Additionally it was hoped that this protocol would lend support to as broad a range of existing and anticipated measurement methods for each structure and feature as possible. The OAI knee-imaging schedule is outlined below in Table 1.

A 3 Tesla MRI system was utilized rather than a 1.5 Tesla system because of the potential advantages of signal-to-noise ratio. The OAI knee MRI protocol had an acquisition time of less than 60 minutes and was enhanced for assessment of quantitative (e.g. cartilage volume) and qualitative measures (e.g. cartilage lesion scores) of OA pathology. Table 2 outlines the knee MRI sequences and scan times in minutes.

OAI Knee Imaging Schedule						
Knee Imaging Protocol	**Screening Visit**	**Enrollment Visit**	**Follow-up**			
			Year 1	Year 2	Year 3	Year 4
Bilateral MRI exam of the knees using 3.0 Tesla Siemens Trio scanners		All	All	All	All	All
Bilateral standing Posterio-anterior "fixed flexion" knee radiographs (both knees on 1 image)	All		All	All	All	All
Bilateral standing Fluoroscopically positioned knee radiographs (one knee per film)		Pr	Pr	Pr		

Table 1 OAI Knee Imaging Schedule. Pr = Progressive sub-cohort. All = Progressive and incidence sub-cohorts[17]

Knee MRI Sequences and Scan Times				
Number	**Scan**	**R Knee**	**L Knee**	**Total**
1	Localiser (3-plane)	0.5	0.5	1.0
2	SAG 3D DESS WE	10.6	10.6	21.2
3	COR IW TSE FS 3200 29	3.4	3.4	6.8
4	SAG IW TSE FS 3200 30	4.7	4.7	9.4
5	COR T1 3D FLASH WE	8.6	-	8.6
6	SAG T2 MAP 120mm FOV	10.6	-	10.6
	Total	**38.4**	**19.2**	**57.6**

Table 2 Knee MRI Sequences and Scan Times (minutes) [17]

Bilateral Standing Fixed-Flexion Posteroanterior Radiography

The posteroanterior (PA) "fixed flexion" knee radiography protocol was used to obtain knee radiographs in all subjects at the baseline screening visit. Those with symptomatic knee OA were assigned to the Progression sub-cohort. Participants in the Incidence sub-cohort were followed throughout the study using the non-fluoroscopic "fixed flexion" protocol.

The "fixed-flexion" protocol was used to assess the radiology of the tibiofemoral knee joint. This protocol provided information about the joint pathology and disease at baseline, the assessment of incident disease and of structural disease progression (i.e. joint space width).

The radiograph protocol consisted of the following:

- Bilateral, standing knee films
    - Performed at baseline and at each of the annual follow-up visits.
- Radiographs recorded in PA projection, with both knees imaged together on 14x17 inch film using a focus-to-film distance of 72 inches
- Knees in 20-30 degrees of flexion with feet internally rotated by 10 degrees.
    - A plexiglass positioning frame was used to fix each of these angels for each subject

The following considerations were used selecting the appropriate combination of acquisition protocols:

1) Weight-bearing with knees in a flexed position was required
    a) For the joint space width to serve as an indirect measure of cartilage thickness

b) To displace intervening joint fluid

c) To bring the opposing cartilage surfaces into contact.

2) Flexion of the knee was required

a) To bring into contact cartilage surfaces that are loaded during normal walking

b) To avoid artifactual increases in apparent cartilage thickness

3) Evidence suggests that alignment of the x-ray beam with the posterior and anterior rims of the tibial plateau margins increases the precision of estimates of joint space loss over time in OA knees and enhances sensitivity to loss of joint space.

Readers at each clinical center were trained to assess the baseline knee x-rays for joint space narrowing and osteophytes, using a classification based on the OARSI atlas grades (as displayed in Table 3). These assessments were used to determine subcohort assignment.

OARSI Atlas Grades for Fixed Flexion Knee X-Rays	
Osteophytes	
0	Normal (OARSI Grade 0)
1	Minute (equivalent to K&L Grade 1)
2	Possible (OARSI Grade 2)
3	Definite (OARSI Grade 3)
Joint Space Narrowing (Medial and Lateral each graded)	
0	Normal
1	Mild Narrowing (OARSI Grade 1)
2	Moderate Narrowing (OARSI Grade 2)
3	Severe Narrowing (OARSI Grade 3)

Table 3 Baseline Knee OA Grading Scheme used for "fixed-flexion" x-rays [17]

The entire clinical, imaging and questionnaire outcome measures and their frequency are outlined in Table 4. The bolded measures are those that specifically relate to the focus of this thesis.

Examination Measures and Frequency						
Measurement	**Screening Visit**	**Enrollment Visit**	**Follow –up Visit**			
			12m	**24m**	**36m**	**48m**
Blood Collection, Fasting		X	X	X	X	X
Urine Collection		X	X	X	X	X
Height	X			X		X
Weight	X	X		X	X	X
Knee size screen for MRI knee coil	X		X	X	X	X
Body size screen for MRI bore	X					
Abdominal circumference		X		X		X
Hand Examination (DIP bony enlargements)	X					
Knee Examination						
- Alignment (by goniometer)		X	X	X	X	
- Anserine bursa tenderness		X	X		X	X
- Effusion		X		X		X
- Flexion contracture and hyperextension		X				
- Tiobiofemoral joint line tenderness		X	X	X	X	X
- Knee flexion pain/tenderness		X				
- Patellar tenderness		X	X	X	X	X
- Patellar quadriceps tenderness/tendinitis		X				
- Patello-femoral crepitus		X	X	X	X	X

- Medial-lateral laxity				X		
- Knee pain location				X		
Blood Pressure		X	X	X	X	X
Heart Rate		X		X		X
Performance Measures (20-m and 400m timed walk)		X	X	X	X	X
MRI						
- MRI Right and left knee		**X**	**X**	**X**	**X**	**X**
- MRI Right and left thigh		**X**	**X**	**X**		**X**
X-Ray						
- Knee: bilateral PA fixed flexion view	**X**		**X**	**X**	**X**	**X**
- Knee unilateral lateral view (both knees)		**X**	**X**		**X**	
- Hip: AP Pelvis view		X	X		X	
- Hand: dominant PA hand		X	X		X	
Questionnaire / Interview Measures						
Demographics		X	X	X	X	X
MRI contraindications	X	X	X	X	X	X
Knee Symptoms						
- Frequency of symptoms and medication use for pain	**X**	**X**	**X**	**X**	**X**	**X**
- Knee Pain (0-10 rating scale)	X	X	X	X	X	X
- WOMAC Score for pain and		**X**	**X**	**X**	**X**	**X**

stiffness						
- KOOS knee pain and symptoms		**X**	**X**	**X**	**X**	**X**
Knee-related function and QOL (for past 7 days)						
- WOMAC physical function		**X**	**X**	**X**	**X**	**X**
- KOOS sport, recreation		X	X	X	X	X
- KOOS quality of life		**X**	**X**	**X**	**X**	**X**
- Global assessment of knee impact		**X**	**X**	**X**	**X**	**X**
- Limitation of activity due to knee symptoms	X		X	X	X	X
- Work Disability		**X**	**X**	**X**	**X**	**X**
Other Joint Symptoms	X		X	X	X	X
Medications taken in the last 7 days for knee symptoms		X	X	X	X	X
History of knee injury	**X**		**X**	**X**	**X**	**X**
History of knee surgery	**X**		**X**	**X**	**X**	**X**
Family history of knee surgery	**X**			**X**		**X**
Fracture history		X	X	X	X	X
Physical activity in last 7 days		X	X	X	X	X

Table 4 Clinical, Imaging and Questionnaire Outcome Measures for the OAI Study[17]

Data Management

A data management system combined decentralized data submission, centralized and remote data editing, and a centralized database structure designed to collect, transfer, and store data for large-scale multi-center clinical study.

After the data was received by the data-coordinating center, it was assessed via automated and manual editing processes and then written to the study database. Data editing and reporting was implemented via a secure study web site housed on a UCSF CC web-serve. Data modifications were made on screen and any changes saved to the database and to a separate audit table.

Non-UCSF collected data, such as imaging quality assurance center data and reading center data were sent to the coordinating center via customized electronic data transfer protocols and the data integrated into the system as appropriate for study use.

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CHAPTER 3

LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE DEVELOPMENT OF RADIOGRAPHIC KNEE OSTEOARTHRITIS:

A SUB-STUDY OF THE OSTEOARTHRITIS INITIATIVE

This chapter contains the following published peer-reviewed publication:

V. L. Johnson, C. K. Kwoh, A. Guermazi, F. Roemer, R. M. Boudrea, T. Fujii, M. J. Hannon, D. J. Hunter. Loss of anterior cruciate ligament integrity and the development of radiographic knee osteoarthritis: a sub-study of the osteoarthritis initiative. *Osteoarthritis and Cartilage.* 2015; Volume 23, pages 882 – 887.

AUTHOR CONTRIBUTIONS

V.L. Johnson and D.J. Hunter conceived and designed the study and the study question, supervised its conduct and take responsibility for the integrity of the work as a whole, from inception to finish.

V.L. Johnson drafted the manuscript

D.J. Hunter, C. K. Kwoh, A. Guermazi, F. Roemer, R. M. Boudreau, T. Fujii, M. J. Hannon were involved in the design and conduct of the POMA study.

All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE DEVELOPMENT OF RADIOGRAPHIC KNEE OSTEOARTHRITIS: A SUB-STUDY OF THE OSTEOARTHRITIS INITIATIVE.

Authors: V.L. Johnson[1,2] C. K. Kwoh[3], A. Guermazi [4], F. Roemer[4,5], R. M. Boudreau[3], T. Fujii[3], M. J. Hannon[3] & D. J. Hunter[1]

Affiliations: [1] Institute of Bone and Joint Research, University of Sydney, Australia [2] School of Medicine, University of Sydney, [3] University of Pittsburgh, Pennsylvania, USA, [4] Boston University School of Medicine, Boston, MA, USA, [5] Klinikum Augsburg, Augsburg, Germany

Corresponding Author: Victoria L Johnson

Abstract

Introduction

Injury to the anterior cruciate ligament (ACL) due to high impact sporting injuries in the adolescent population is strongly linked to the subsequent development of osteoarthritis. However, it is unknown whether a similar relationship exists in an older population. The aim of this study was to determine whether loss of ACL integrity in an older cohort precedes the onset of radiographic OA (ROA).

Methods

Participants in this nested case-control study were selected from the Osteoarthritis Initiative (OAI) study who had risk factors for OA development but did not have ROA in both knees at baseline. Knees selected for this study had radiographs with a Kellgren-Lawrence grading (KLG) of 0 or 1 at baseline. Participants were examined annually with radiographs and non contrast-enhanced magnetic resonance imaging (MRI) performed using the OAI protocol, over a 4-year period. The MRIs were assessed for the presence of ACL tears. Case knees were defined by the development of ROA (i.e. Kellgren and Lawrence grade >=2) on the postero-anterior knee radiographs between the 12month to the 48 month visits. Their radiographs were assessed at P0 (time of onset of radiographic knee OA), 1 year prior to P0 (P-1) and at baseline. Controls were selected from amongst those who did not develop incident ROA and were matched to cases on sex, age (within five years), contralateral knee OA status, and time since enrollment in the OAI.

Results

355 persons who developed ROA were matched to 355 controls. A total of 16

participants had either a complete or partial tear in their ACL. No relationship between loss of ACL integrity and incident ROA was found at any assessment time point. Odds ratios (OR) for baseline, one year prior to incident ROA (P1) and at point of occurrence of incident ROA (P0) were 2.00 (0.66-6.06), 2.5 (0.76-8.24) and 2.75 (0.85-8.88) respectively. A significant risk of incident ROA was found in participants who had a history of knee injury with an OR of 1.51 (1.05-2.16).

Conclusion

Loss of ACL integrity does not confer a significantly increased risk of incident ROA in an older adult cohort. In contrast, a history of knee injury was associated with an increased risk of incident ROA.

Introduction

Despite the introduction of biomechanical training programs in schools and elite sporting organisations[1, 2] the knee remains one of the most commonly injured joints. In the context of osteoarthritis the most important injuries are those resulting in the rupture of the anterior cruciate ligament (ACL), which is responsible for restraint of anterior tibial translation, as it is often accompanied by damage to the articular cartilage, subchondral bone, menisci and collateral ligaments.

The risk of ACL rupture is higher in adolescents and up to 70% higher in high-risk sports than in the general population[3]. ACL rupture is strongly linked to the subsequent development of OA with a substantial percentage of patients showing OA changes and functional disability as early as 10 years after the initial injury[3, 4]. It is thought to account for up to 15% of a person's risk of developing knee OA however it typically occurs in adolescents and young adults[3]. At the present time, no study has established whether a similar relationship between ACL injury and incident OA exists in an older adult cohort. ACL deficiency causes increased translational shear force on the cartilage and in combination with age, is one of the strongest predictors of OA[5], this could confer an increased risk of OA development.

The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. Persons with ACL tears have been shown to be at an increased risk for cartilage loss [6], meniscal degeneration, osteophyte formation and bone marrow lesions (BMLs) [7] with the pattern of damage being consistent with the initial

location of osteochondral injury of an ACL rupture in the lateral tibiofemoral compartment [8].

Although radiographic features such as joint space narrowing and the presence of osteophytes define the presence of radiographic OA (ROA), magnetic resonance imaging (MRI) may improve the assessment of early disease development and progression. MRI has shown a higher specificity and sensitivity for the assessment of joint morphology [9] and the diagnosis of post-traumatic degenerative changes [10, 11]. Thus MRI may improve the assessment of early disease development preceding the development of either joint space narrowing or osteophyte formation on a plain radiograph. At this point the underlying structural changes that predate the development of ROA remain under examined [12].

Therefore, the aims of this study were to identify whether a similar relationship between ACL injury and radiographic knee OA that as been reported elsewhere in an adolescent cohort[3, 4] also exists in an older adult cohort. Furthermore, whether a history of knee injury in an older adult cohort results in an increased risk of incident radiographic knee OA.

Patients and Methods

Study Design and Subjects

The study participants were selected from the Osteoarthritis Initiative (OAI), which is a multi-centre, ten-year, longitudinal, prospective observational cohort study designed to identify biomarkers and risk factors for knee OA causation and progression. 4,796 study subjects underwent a detailed assessment annually, including physical examination, and interview using self-reported measures, such as joint pain and disability as well as knee MRIs and radiographs. Covariates including body mass index, muscle strength, and physical activity were collected in tandem with the outcome assessments. Details of subject inclusion and exclusion have been described elsewhere[13] however, individuals with bilateral end-stage knee OA, knee arthroplasty, or bilateral radiographs with Kellgren and Lawrence (KLG) grade 4, and inflammatory arthritis were excluded from the study population.

The individuals for this sub-study were selected from those who did not have bilateral radiographic knee OA at enrolment (i.e. Kellgren-Lawrence grading (KLG) of 0 or 1. Some individuals who were selected to this cohort had frequent knee pain but did not have radiographic tibio-femoral OA at enrolment [14].

Cases and Controls

Cases were defined as study participants who had at least one knee that developed incident ROA; i.e. the first occurrence of radiographic findings compatible with OA (KLG of ≥2 on the PA view) [15] from baseline to the 48 month visit. The first occurrence of ROA was called time point P0. The 12 month time point before ROA was called P1.

The same number of controls were selected from the participants who did not develop incident ROA during the study period and matched to cases knees on sex, age within 5 years and contralateral knee status (i.e. KL = 0,1, or 2+ in the other knee). Each case was matched to a sample of those who are at risk at the time of case occurrence, whether this be at 12, 24, 36 or 48 months of follow-up. Both cases and controls were KLG 0 or 1 at baseline and the case knee had to display no radiographic signs of incident OA to be eligible as a control.

Radiographs

Radiography of both knees was performed in all subjects. The radiographs of knees were assessed for their KLG [16]. Radiographs acquired at baseline, 12, 24, 36 and 48-month visits were read by the OAI central readers for KLG of ≥2 (case definition) [16] on the postero-anterior (PA) knee radiographs.

A total of 355 participants who displayed KLG of 0 or 1 at baseline, went on to develop radiographic signs of knee OA at relevant time points (defined as KLG ≥2 on the PA fixed-flexion radiographs with incidence cases not having any definitive joint space narrowing).

MRI sequence parameters

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites. Non-contrast enhanced MRIs of both cases and controls from enrolment and the visits prior to and when meeting case and control definitions, were read.

The MRI pulse sequence protocol included a coronal two-dimensional intermediate-weighted (IW) turbo spin-echo [17], sagittal three-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multiplanar reformations of the 3D DESS and sagittal IW fat saturated (FS) TSE sequences. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail [13].

The MRI Osteoarthritis Knee Score (MOAKS) system was used to assess the whole joint for structural changes compatible with knee OA [9]. MRI readings were performed by AG and FWR with 14 and 11 years experience in MRI semi-quantitative assessment respectively. Scores were entered directly into an electronic web-based database. All MRIs were read sequentially and un-blinded to time point, but blinded to case/control status. Inter-rater calibration and reliability-testing on a subset of MRI scans was performed for MRI reading quality control. Subsequently, ongoing surveillance for measurement drift was carried out by AG by re-reading 5% of the MRIs.

ACL tears

Sagittal and coronal views were used to detect the presence of an ACL tear at baseline and scored on a 0-2 scale (0= normal, 1 = partial tear and 2 = complete tear). A tear was defined as complete when complete disruption of ACL fibres and ligament discontinuity were noted, whilst residual straight and tight ACL fibres in at least one-pulse sequence was defined as a partial tear. Since partial tears may change the joint biomechanics and thus the pattern of joint damage, partial and complete tears have been combined. Figure 1 shows an example of an ACL tear that occurred between baseline and P0, as visualized on MRI. All MRIs were read by a single board-certified

musculoskeletal radiologist, separate from the scoring of other joint features and blinded to the hypothesis being tested.

Selection of knees for inclusion

All incident knees were classified into one of five strata based on the baseline KLG status in both knees. Strata A was participants who had KLG=0 for both knees. Strata B for KLG=0 in one knee and KLG=1 in the other. Strata C for KLG=1 in both knees. Strata D for those with KLG=0 in one knee and KLG≥ 2 in the other and strata E for participants who had KLG=1 in one knee and KLG≥to 2 in the other.

Assessment of joint injury

History of previous injury to the knee was evaluated at the enrolment visit by asking the participants whether they have ever injured their knee(s) badly enough to limit their ability to walk for at least two days.

Statistical analysis

Conditional logistic regression models were employed to model the relationships between the key predictors and OA. A GEE (general estimated equations) method with a robust sandwich estimator was used to account for the correlations between knees for cases of bilateral incident OA or two knees from the same individual used as controls.

The ACL tear predictors and their odds-ratios were modelled; the time point concurrent with incident ROA (P0), the time point one-year prior to incident ROA (P1) and baseline.

Results

The demographics and baseline clinical parameters are listed in Table 1. Sixty-six percent of the study population were women, the average age of the case subjects was 60.1 years with a standard deviation (SD) of 8.6, with the average age of the matched controls being 60.0 years with a SD of 8.4. The mean BMI was 28.9 kg/m^2 (SD 4.5) and 27.7 kg/m^2 (SD 4.4) for cases and controls, respectively and this difference was significant ($p = .0003$).

A total of 16 study participants demonstrated either a partial or complete ACL tear, of which 15 study participants had either partial or complete ACL tears at baseline. Of these 15 tears present at baseline, 14 ACLs were graded as partially torn (4 controls and 10 cases) and 1 participant in the control group was graded as completely torn. The remaining ACL tear occurred in a participant in the case group who was noted to have partially torn their ACL at the P0 time point. The timing of onset of ROA (not the timing of the ACL tear) with the number of subjects who developed ROA at each time point is illustrated in Figure 2. Of the 710 study participants, a history of knee injury was reported in 63 controls and 89 cases at baseline.

Results of the effect of ACL tear and history of injury on the incidence of knee OA can be found in Table 2. No significant relationship between radiographic incident OA and rupture of the ACL was found at any of the observed time points (P1 OR = 2.50, 95% CI = 0.76-8.24; P0 OR = 2.75, 95% CI = 0.85-8.88). Only in participants who reported having a history of knee injury at baseline (OR = 1.51, 95% CI = 1.05 – 2.16) was a significantly increased risk of developing incident radiographic knee OA found.

		Total (N=710)		Controls (N=355)		Cases (N=355)	
		N	**%**	**N**	**%**	**N**	**%**
Participant Demographics							
Gender	Male	236	33.24	118	33.24	118	33.24
	Female	474	66.8	237	66.8	237	66.8
Mean Age		60.1±8.5		60.0±8.4		60.1±8.6	
Mean BMI		28.3±4.5		27.7±4.4		28.9±4.5	
Strata Class							
	A	126	17.75	63	17.75	63	17.75
	B	152	21.41	76	21.41	76	21.41
	C	166	23.38	83	23.38	83	23.38
	D	118	16.62	59	16.62	59	16.62
	E	148	20.85	74	20.85	74	20.85
Baseline Kellgren and Lawrence (grades 0/1)							
	0	266	37.46	133	37.46	133	37.46
	1	444	62.54	222	62.54	222	62.54
Injury at Baseline							
		152	21.41	63	17.75	89	25.07

Table 1: Baseline characteristics of the cases and controls in the study population

	Total (N=710)		Controls (N=355)		Cases (N=355)			
	N	%	N	%	N	%	OR	95% CI
ACL Tear at Baseline								
No Injury	695	97.89	350	98.59	345	97.18	1.00	
Partial Tear	14	1.97	4	1.13	10	2.82	2.00	0.66-6.06
Complete Tear	1	0.14	1	0.28				
ACL Tear Present 12 months prior to Radiographic Incidence (P1) N=660								
No Injury	646	97.88	326	98.79	320	96.97	1.00	
Partial Tear	13	1.97	3	0.91	10	3.03	2.50	0.76-8.24
Complete Tear	1	0.15	1	0.30				
ACL Tear Present at Radiographic Incidence (P0) N=670								
No Injury	655	97.76	331	98.81	324	96.72	1.00	
Partial Tear	15	2.09	4	0.90	11	3.28	2.75	0.85-8.88
Complete Tear	1	0.15	1	0.30				
Baseline Injury								
	152	21.41	63	17.75	89	25.07	1.51	1.05 - 2.16

Table 2: Conditional logistic regression analysis for occurrence of incident radiographic OA due to ACL tears in the study population

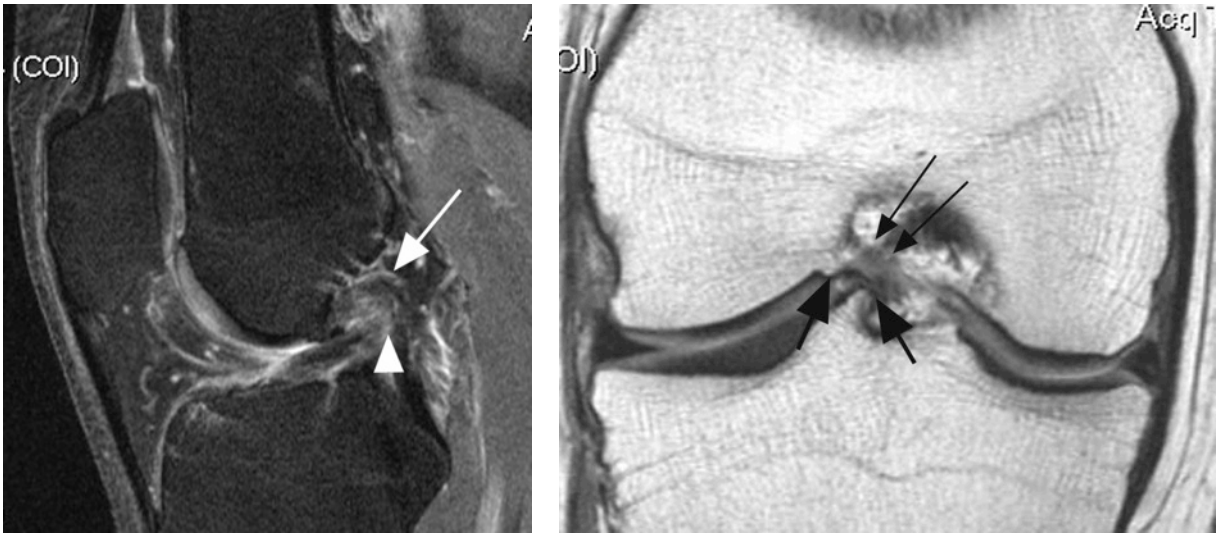

Figure 1. Prevalent anterior cruciate ligament (ACL) tear in a 61-year-old male participant. A. Sagittal fat saturated intermediate-weighted MR image shows complete disruption of ACL (arrowhead). Note also increased bowing of posterior cruciate ligament (arrow), an indirect sign of ACL damage and potential joint instability. ACL damage may be prevalent in osteoarthritis without recall of previous injury. B. Coronal intermediate-weighted image shows complete rupture of ACL with only remnant fibers visible (thin arrows). Likely etiology of non-traumatic ACL disruption in this case was chronic friction of tibial spine and femoral notch osteophytes. Note absence of osteophytes at the joint margins.

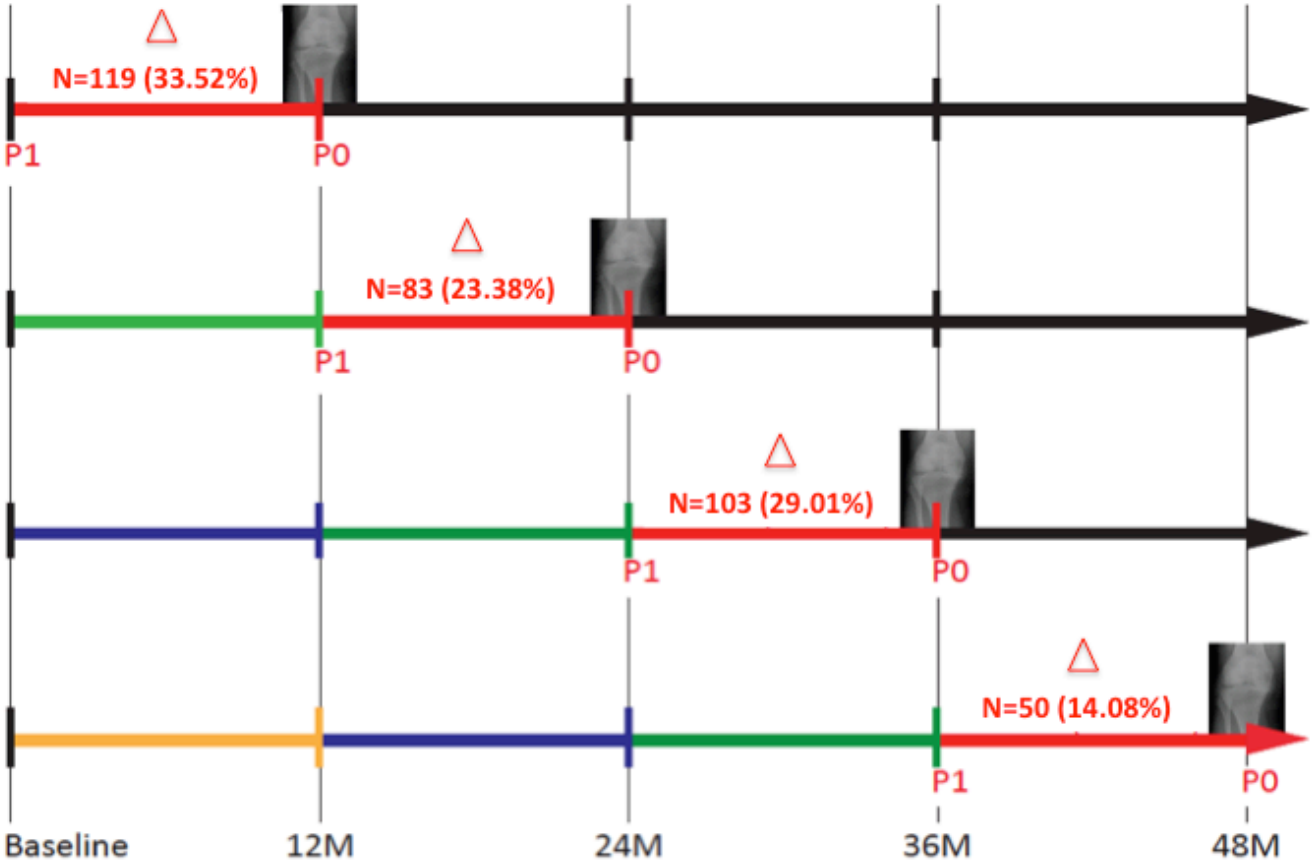

Figure 2: Schema detailing the timing of onset of ROA with the number of subjects who developed ROA at that time point.

Discussion

The results presented show that, in an older adult cohort, an ACL tear is an infrequent event that does not appear to significantly predispose an individual to incident knee ROA.

Traumatic knee injuries involving ACL rupture are the most common form of knee injury and due to its high incidence in adolescents [3, 18], it has been widely studied due to its potential for the subsequent development of OA as well as functional disability as early as 10 years after the initial injury[3, 4]. A review by Oiestad [17] reported a prevalence of knee OA of 13% for subjects who suffered from an isolated traumatic injury of the ACL. Our study also demonstrated that participants who reported a history of knee injury, or who had an observable injury at baseline testing conferred a significant risk of developing incident knee ROA.

However, whilst it has been well documented that a younger cohort have a significantly increased risk of developing knee OA post ACL injury, it has not been widely documented whether an ACL injury in older cohorts, in which OA is more prevalent, carries a similar risk. This study demonstrated that in an older cohort having a partial ACL tear, whether it is a partial or complete, does not lead to a statistically significantly increased risk of incident ROA. A similar result was found by the only other paper to have investigated this question. Amin et al [19] found that a complete ACL tear did increase the risk for cartilage loss at the medial tibiofemoral compartments. However, following adjustment for the presence of medial meniscal tears there was no further increased risk for cartilage loss. Thus it was concluded that

individuals with knee OA and an incidental complete ACL tear did not confer an increased risk for cartilage loss above that of what is mediated by meniscal pathology.

One potential reason for this difference has been suggested in a study by Hasegawa et al [20] which identified degenerated ACLs in knees without cartilage degeneration. It was shown that inflammatory cells existed between collagen fibers within the ACL substance, regardless of the presence of cartilage degeneration. This indicated that an inflammatory process is driven by ACL intrinsic mechanisms that are linked explicitly with ageing. Therefore, these degenerative ligamentous changes may contribute to the increased fragility of the ligament thus predisposing it to tearing or rupture from minor trauma independent of the cartilage, osteochondral or meniscal changes associated with OA. These findings are particularly relevant to this study because where an ACL tear was observed on MRI in participants in this study were not linked to a prior significant injury, thus suggesting that many of these tears were degenerative in nature.

Another reason for the differences between these two populations could be due to the nature of the injury. In adolescents the majority of ACL injuries occur during sporting activities that involve pivoting and jumping. These injuries usually involve large impact forces and most often result in injury not only to the ACL but also to the meniscus and articular cartilage with a subsequent development of BMLs [4]. It is these large forces that are responsible for the majority of tissue damage [21]. It has been shown that occult osteochondral lesions of the posterolateral tibial plateau are seen on MRI in 80-90% of patients with an acute ACL injury suggesting that articular cartilage sustains a considerable impact at the time of injury [8]. Oiestad et al [17]

proposed that the prevalence of OA due to ACL rupture with concomitant meniscal damage might be as high as 40%.

Injury to the ACL in the elderly population would not require large forces when considering the aforementioned ligamentous degenerative changes. Without these large forces being imparted on the joint, there may be no associated injury to the meniscus or underlying articular cartilage at the time of ACL rupture. Thus it is likely that incidental tears to the ACL do not impact upon other joint tissues and as such do not contribute to the pathological processes of knee OA.

Limitations

The frequency of ACL tears in this study sample was smaller than previously described in the literature with 1 complete ACL tear and 15 partial ACL tears with a tear rate of 2.25% in the whole study population. Previous studies investigating ACL tears in individuals with established knee ROA presented rates of ACL full-thickness tears ranging from 22 – 35% [22, 23]. This decreased prevalence of ACL tears may be related to the selection factors used to define the 355 participants chosen from the OAI study to become part of this sub-study. The fidelity of MRI in ACL diagnosis has accuracy between 90 and 100% compared to knee arthroscopy, which is the gold standard [24, 25], but is yet to be demonstrated in patients with knee OA. Such misclassification would bias towards a null result, so our findings may underestimate the true associations.

Having only 16 participants out of a sample size of 710 suffer from a complete or partial ACL tear makes this a small sample size. This would explain why the point

estimate OR at baseline, P0 and P1 were substantial yet the 95% CI did not produce significance. Furthermore, MRI appears to be limited in the diagnosis of partial tears, and thus there is a possibility that other participants with partial tears may have been missed [26]. Hence, these results need to be confirmed in a larger cohort.

Finally, the relationship between partial ACL tears and the development of incident OA is uncertain and not well documented. As the majority of tears observed in this study were rated as 'partial' comparisons between our study and with studies of complete tears are therefore of limited significance.

Conclusion

In summary, the loss of ACL integrity on MRI imaging may not confer a significantly increased risk of incident ROA in an older adult cohort. Our study only found that patients who had a history of knee injury had an increased risk of incident ROA. Further longitudinal research is required to corroborate these findings.

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CHAPTER 4

DOES AGE INFLUENCE THE RISK OF INCIDENT KNEE OSTEOARTHRITIS FOLLOWING TRAUMATIC ANTERIOR CRUCIATE LIGAMENT INJURY?

This chapter contains the following published peer-reviewed publication:

V.L. Johnson, J Roe, L Salmon, L Pinczewski, D.J. Hunter. Does age influence the risk of incident knee osteoarthritis following traumatic anterior cruciate ligament injury? *American Journal of Sports Medicine* 2016; Volume 44, pages 2399 – 2405.

AUTHOR CONTRIBUTIONS

V.L. Johnson designed the study question and drafted the manuscript

V.L. Johnson and D.J. Hunter conceived and designed the study, supervised its conduct and take responsibility for the integrity of the work as a whole, from inception to finish.

Justin P Roe, Lucy J Salmon, Leo A Pinczewski were involved in the design and conduct of the North Sydney Orthopaedic and Sports Medicine study.

Leo A Pinczewski was the primary orthopaedic surgeon for each of the cases.

All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

DOES AGE INFLUENCE THE RISK OF INCIDENT KNEE OSTEOARTHRITIS FOLLOWING TRAUMATIC ANTERIOR CRUCIATE LIGAMENT INJURY?

Authors: Victoria L Johnson[1,2], Justin P Roe[3], Lucy J Salmon[3], Leo A Pinczewski[3], and David J Hunter[1,4]

Affiliations

[1]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Australia

[2]The Sydney Medical School, University of Sydney

[3]The Mater Clinic, North Sydney Orthopaedic and Sports Medicine Centre, Sydney, New South Wales, Australia.

[4]Rheumatology Department, Royal North Shore Hospital, Sydney, Australia.

Corresponding Author: Victoria L Johnson

Abstract

Background

The development of radiographic knee OA following ACL rupture has long been studied and proven in the adolescent population. However, similar exhaustive investigations have not been conducted in mature-aged athletes or in older populations.

Hypothesis

The primary aim of this study was to identify whether an older adult population had an increased risk of incident radiographic knee OA following traumatic knee injury compared to a young-adult population.

Study Design

Cohort Study

Methods

Patients with ACL ruptures who underwent primary reconstruction were enrolled in a prospective longitudinal single center study over 15 years. The adult cohort was defined as participants who had a knee injury resulting in an ACL tear aged 35 years or older, the adolescent-young cohort suffered similar knee injuries and were aged 25 years and younger and a third cohort of participants aged 26-34 years who suffered a knee injury were included to identify the existence of any age-related dose-response relationship for the onset of radiographic knee OA. A Kaplan-Meier survival analysis was employed to determine the occurrence of incident radiographic OA across the

study populations at 2-, 5-, 10- and 15-years post reconstruction. Significance at each time point was analysed using Chi-squared tests.

Results

A total of 215 patients, 112 adolescent (average age 20.4years, 51% female) and 32 adults (average age 40.2years, 55.9% female) were assessed for International Knee Documentation Committee (IKDC) grading on knee radiographs. It was found that 53% and 78% of adults at ten and fifteen years post reconstruction had an IKDC grade of B or greater respectively compared to 17.7% and 61.6% of the adolescent-young cohort. Chi-square testing found that adults developed OA earlier than adolescents at 5- and 10-years post-reconstruction (p-value = 0.017 and <0.0001). However, survival analysis did not demonstrate that adults were more likely to develop radiographic knee OA 15-years post reconstruction compared to the adolescent-young cohort (p-value = 0.4).

Conclusion

The age at which an ACL injury is sustained does not appear to influence the rate of incident radiographic knee OA although mature age athletes are likely to get to the OA endpoint sooner.

Introduction

Rupture of the anterior cruciate ligament (ACL) is a common cause of severe knee injury which affects physically active men and women as the ACL is essential for knee kinematics by functioning as the main restraint of anterior tibial translation and acts as an anterior-posterior stabilizer[4].

ACL injuries occur with an annual incidence of 81 per 100,000 persons aged between 10 and 64 years[5], with the risk of rupture highest amongst adolescents who participate in high-risk sports. As the majority of these injuries occur in a younger population the long-term consequences of prolonged disability due to joint instability, meniscal and chondral surface damage and thus subsequent OA development means these injuries carry a large financial and health encumbrance both due to pain and loss of physical functioning[18]. Traumatic lesions to the ACL are a well-known risk factor for OA[4, 10], with radiographic changes suggestive of OA[6, 10] having been reported as early as 10 years following the initial injury in up to 70% of young adults who sustained injury to their ACL[12, 14, 16]. This equates to a risk of OA incidence up to 5-times greater when compared to cohorts which have never suffered a knee injury[6].

The subsequent development of radiographic knee OA following ACL rupture has long been studied and proven[5, 6, 10, 14, 16] in the adolescent population. However, similar exhaustive investigation has not been conducted in mature-aged athletes and in older populations.

Age is one of the strongest predictors of OA, however the exact mechanism is poorly understood. A combination of changes including the capacity for joint tissues to adapt to biomechanical insults, biological changes such as cellular senescence and a reduced capacity to adjust to biomechanical challenges are likely contributing factors[3].

Knowledge of the course of development of cartilage damage after knee ligament injury is required when new methods of treatment are to be evaluated and when disease development is to be compared with other populations with OA. This type of information is also helpful in adequately informing patients about their likely prognosis.

Therefore the aims of this study were to identify whether an older adult population has an increased risk of incident radiographic knee OA following ACL reconstruction compared to an adolescent population and whether older adults are at an increased risk of developing more severe radiographic knee OA.

Methods

Study Design and Participants

A total of 215 patients with ACL ruptures who underwent primary reconstruction with hamstring autografts between October 1993 and March 1996 were enrolled in this prospective-longitudinal, single center study over 15 years.

Three study populations were selected. The adult cohort (cases) were defined as study participants who had a knee injury resulting in an ACL tear and aged 35 years or older. The adolescent-young cohort (controls) were study participants with a similar history of knee injury and ACL tear and aged 25 years and younger. An additional cohort of participants' aged 26-34 years was included to check for the existence of any age-related dose-response relationship for the onset of radiographic knee OA.

Exclusion criteria

Participants were selected for this study if the injury to their ACL excluded any other associated ligamentous injury requiring surgical management, any pre-existing significant chondral damage or degeneration as seen on x-ray prior to surgery, prior meniscectomy, excision of one third or more of 1 meniscus and no meniscal instability, pre-operative abnormal radiological findings, an abnormality in the contralateral knee, patients seeking compensation for their injuries, and those who did not wish to participate in a research program. A local independent ethics committee granted ethical approval.

Participants with a new acute injury were assessed clinically and a diagnosis made on the basis of clinical findings including Lachman, pivot-shift and instrumented laxity tests on both knees.

Knee Injury

All of the ACL injuries measured in this study were sustained whilst each of the individuals were involved in high-impact sporting activities. The majority of injuries were sustained playing soccer, rugby union, rugby league, skiing and netball.

Surgical Technique

All procedures were performed by JPR. The technique was standardized for all patients. A 4-strand gracilis and semitendinosus tendon graft was used, and the tunnel diameter equaled the measured diameter of the graft (range, 6-9mm).

The femoral tunnel was drilled before the tibial tunnel via the anteromedial arthroscopic portal, with the knee in maximal flexion, and positioned 5mm anterior to the posterior capsular insertion at the 10:30 or 1:30 O'Clock position depending whether the index knee for an individual was right or left. The tibial tunnel was centered on a line between the anterior tibial spine and the posterior margin of the anterior horn of the lateral meniscus, half a graft diameter lateral along that line. In all cases, the fixation consisted of a 7x25-mm titanium cannulated interference screw (RCI, Smith & Nephew Endoscopy, Andover, Massachusetts) for both femoral and tibial fixations. By 6 weeks, jogging in a straight line, swimming and cycling were permitted. After 12 weeks, general strengthening exercises were continued. Return to competitive sport involving jumping, pivoting, or side-stepping was discouraged until

9 months after reconstruction and a successful return to sport programme had been completed.

ACL Graft Rupture

During the course of the study, 25 participants suffered a rupture of their ACL graft and this was confirmed at the time of revision ACL surgical reconstruction. The diagnosis of an ACL graft rupture was based on clinical findings of a positive pivot-shift examination and/or Lachman test result (grade 2 or more). Participants who suffered a graft rupture and/or subsequent revision surgery remained in the study.

Injury to the Meniscus

A total of 100 participants suffered concomitant injury to their meniscus at the time of ACL rupture, as seen in Table 1. Injury to the meniscus was determined arthroscopically at the time of ACL reconstruction.

Radiographs

Radiographic assessment was conducted at 2, 5, 10 and 15 years postoperatively with weight-bearing anteroposterior, 30 degrees of flexion posteroanterior, lateral, and patellofemoral views. Radiographs were classified according to the International Knee Documentation Committee (IKDC) guidelines as follows: A, normal; B, minimal changes but detectable joint space narrowing; C, moderate changes and joint space narrowing of up to 50%; and D, severe changes and more than 50% joint space narrowing. The worst grade in any compartment determines the overall IKDC radiographic grade. For the purposes of this study radiographic OA was defined as an IKDC grade of B or greater.

Statistical Analysis

Statistical analyses were performed using SPSS software. A Kaplan-Meier survival analysis was employed to determine the occurrence of incident radiographic OA in all three study populations and to model the relationships between the key predictors (IKDC radiographic scoring) and OA, concurrent with each of the time points of 2-, 5-, 10- and 15-year postoperative follow-up. The results were then plotted in a survival curve to determine if a dose-response relationship existed between age and incidence of radiographic OA. The survival curves of each study population were compared using a Wilcoxon Log-Rank test. Chi-squared tests were then used to compare the incidence of radiographic osteoarthritis at each of the follow-up time-points. Statistical significance was set at 0.05.

Results

The demographics and baseline clinical parameters are listed in Table 1. Forty-nine percent of the study population was female, the average age of the adult cohort was 40 years at the time of ACL reconstruction, with a standard deviation of 4.5 (range 35 – 58 years), with the average age of the adolescent-young cohort being 20 years with a standard deviation of 3.2 (age range 13 – 25 years). Fifty-three percent of adults and forty-nine percent of adolescent-young participants injured their right knee. A concomitant meniscal tear was noted in 16 of adult (50%) and 55 adolescent (49%) participants. Participants who presented with re-injury to their ACL (i.e. rupture of the ACL graft) was highest amongst the adolescent-young cohort, with 21 participants (18.8%) compared to 2 (6%) in the adult cohort (p-value = 0.09) and 2 (2.8%) in the cohort of participants aged 26-34years (p-value = 0.001). Further to this, during the 15 year study period 12 adolescents (9.3%), 5 adults (6.4%) and 7 participants aged 26-34 years (10.1%) suffered further meniscal injuries requiring surgical correction. The breakdown of the IKDC radiographic grading at each time point is displayed in Table 2. Only one adult participant had radiographic features of OA two years postoperatively. A higher percentage of adult participants developed radiographic OA at each of the five-, ten- and fifteen years postoperative time points when compared to the adolescent-young cohort. Thirty-eight percent of adults had an IKDC radiographic grade of B at five-years post operation, as compared to only 7.8% of adolescents (p-value = 0.017). At ten and fifteen years 53% and 78% of adults had a radiographic IKDC grade of B or greater respectively (p-values o f <0.0001 and 0.06 respectively). In comparison, 17.7% and 61.6% of adolescents had an IKDC grading of B or greater at ten- and fifteen-years postoperatively respectively. Additionally, significance is

not reached when combining A and B grades against C and D grades of the adult and adolescent-young cohorts at 15 years ($p = 0.66$).

The Kaplan-Meier survival analysis for the incidence of radiographic knee osteoarthritis for adult, adolescent-young and additional cohorts is displayed in Figure 1 and Table 3. Two years post-operation adults had a survival estimate of 0.97 (95% CI 0.82 – 1.0) against the adolescent participants of 1.0 (95% CI 0.96 – 1.0). Adult participants had survival estimates of 0.84, 0.69 and 0.19 whilst adolescents participants had estimates of 0.96, 0.89 and 0.48 for adolescents at five-, ten-, and fifteen- years post-operation respectively. Whilst it appeared from the survival estimates that adults were more likely to develop radiographic OA, log-rank analysis found no statistical significance between the two curves (p-value = 0.4).

Chi-squared testing showed that only at 5-years and 10-years post reconstruction did the difference in OA incidence between the adult (38%) and adolescent-young cohorts (8%) reach significance (p-value =0.017 and $p = <0.0001$ respectively). This trend did not continue, however, as at 15-years post reconstruction the difference between the two cohorts (78% versus 62%) was no longer significant (p-value = 0.06).

Additionally, as displayed in Table 2, it was found that a greater proportion of adults (74.1%), the adolescent-young cohort (54.7%) and those aged 26-34 (62.5%) developed OA (IKDC grading of B or greater) in the medial compartment compared to the lateral compartment at 15 years following reconstruction. Osteoarthritis in the lateral compartment was only recorded in approximately a third of each of the adult (33.3%), adolescent-young (39%) and individuals aged 26-34 years (37.5%) cohorts.

Patellofemoral OA was also noted in approximately one-third of all individuals (adults: 40.7%, adolescents-young: 30.9%, individuals aged 26-34 33.9%).

Participants aged 26-34 years were included in the survival analysis to see if an age dose-response relationship was evident. Again, significance was reached only at 2 years and 5-years post reconstruction time-point between these participants aged 26-34years and with the adolescent-young cohort (p-value 0.004 at 2 years and 0.04 at 5 years respectively, Table 2). At no point did the participants in the 26-34 years group reach significance with the adult cohort using chi-squared testing. At 15-years post reconstruction there was no significant difference when comparing the survival curves of any of the three cohorts for radiographic knee OA incidence. Wilcoxon Log-Rank testing producing p-values of 0.97 and 0.37 when comparing the 26-34 cohort to the adult cohort and adolescent-young curves (p=0.37) respectively.

	Total (N= 215)	Adolescent-Young Cohort (N= 112)	Participants Aged 26 – 34 (N = 71)	Adult Cohort (N = 32)
Mean age (SD)	30 years	20.4 ± 3.2	29.2 ± 2.5	40.2 ± 4.5
Female sex-no. (%)	76 (49.1%)	57 (51.0%)	30 (42.2%)	19 (55.9%)
Injury to right knee (%)	72 (50.9%)	55 (49.1%)	38 (53.5%)	17 (53.1%)
Injury to either meniscus	100 (45.9%)	55 (49.1%)	29 (39.2%)	16 (50%)
ACL Graft Re-rupture	25 (11.5%)	21 (18.8%)	2 (2.7%)	2 (6.3%)

Table 1: Study Demographics

IKDC Grading	**X-Ray Medial**		**X-Ray Lateral**		**X-Ray PF**		**Overall Grading**		**Chi-Squared p-value for Overall IKDC Grading**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
2- Year Follow up									
Adults									
A	16	93.4	17	100	17	100	16	94.1	Adults: Adolescent-Young p = 0.73
B	1	6.3					1	5.9	
C									
D									
Not Assessed = 15									
Adolescents									
A	69	100	69	100	69	100	76	100	Adolescent-Young: Aged 26-34 **p = 0.004**
B									
C									
D									
Not Assessed = 36									
Aged 26- 34									
A	35	81.4	40	93.0	40	93.0	38	88.4	Adults: Aged 26-34 p = 0.4
B	6	14.0	1	1.9	1	1.9	5	11.6	
C									
D									
Not Assessed = 28									
5- Year Follow up									
Adults									Adults: Adolescent-Young **p = 0.017**
A	9	64.3	11	84.6	12	92.3	8	61.5	
B	5	35.7	2	15.4	1	7.7	5	38.5	
C									

D									
Not Assessed = 19									
Adolescents									
A	49	96.1	50	98.0	51	100	47	92.2	Adolescent-Young: Aged 26-34 **p = 0.04**
B	2	3.9	1	2.0			4	7.8	
C									
D									
Not Assessed = 61									
Aged 26-34									
A	34	81.0	39	92.9	41	97.6	33	78.6	Adults: Aged 26-34yrs p = 0.53
B	8	19.0	3	7.1	1	2.4	8	19.0	
C									
D									
Not Assessed = 28									
10- Year Follow up									
Adults									
A	9	52.9	14	82.4	15	88.2	8	47.0	**Adults: Adolescent-Young p = <0.0001**
B	7	41.2	3	17.6	2	11.8	8	47.0	
C	1	5.9					1	6.0	
D									
Not Assessed = 15									
Adolescents									
A	50	84.7	54	93.1	58	100	48	82.3	Adolescent-Young: Aged 26-34 p = 1.0
B	9	15.3	4	6.9			1	17.7	
C									
D									
Not Assessed = 53									
Aged 26- 34									Adults: Aged 26-34
A	40	72.7	50	90.9	50	90.9	39	70.1	

B	12	21.8	4	7.3	5	9.1	14	25.5	p = 0.54
C	2	3.6	1	1.8			2	3.6	
D									
Not Assessed = 16									
15- Year Follow up									
Adults									
A	8	29.6	18	66.7	15	59.3	6	22.2	Adults: Adolescent-Young p = 0.06
B	15	59.3	9	33.3	12	40.7	17	63.0	
C	4	14.8					4	14.8	
D									
Not Assessed = 5									
Adolescents									
A	39	45.3	53	61.0	60	69.0	33	38.4	Adolescent-Young: Aged 26-34 p = 0.65
B	41	47.7	31	35.6	25	28.7	43	50.0	
C	6	7.0	2	2.3	1	1.1	8	9.3	
D			1	1.1	1	1.1	2	2.3	
Not Assessed = 26									
Aged 26-34									
A	21	37.5	35	62.5	37	66.1	20	35.7	Adults: Aged 26-34 p = 0.15
B	26	46.4	19	33.9	18	32.1	27	48.2	
C	9	16.1	2	3.6	1	1.8	9	16.1	
D									
Not Assessed = 15									

Table 2: IKDC Grading throughout the study. The IKDC Grading scores are as follows; A, normal knee with no features of radiographic OA; B, minimal changes and barely detectable joint space narrowing; C, moderate changes and joint space narrowing of up to 50%; and D, severe changes and more than 50% joint space narrowing. PF = Patellofemoral

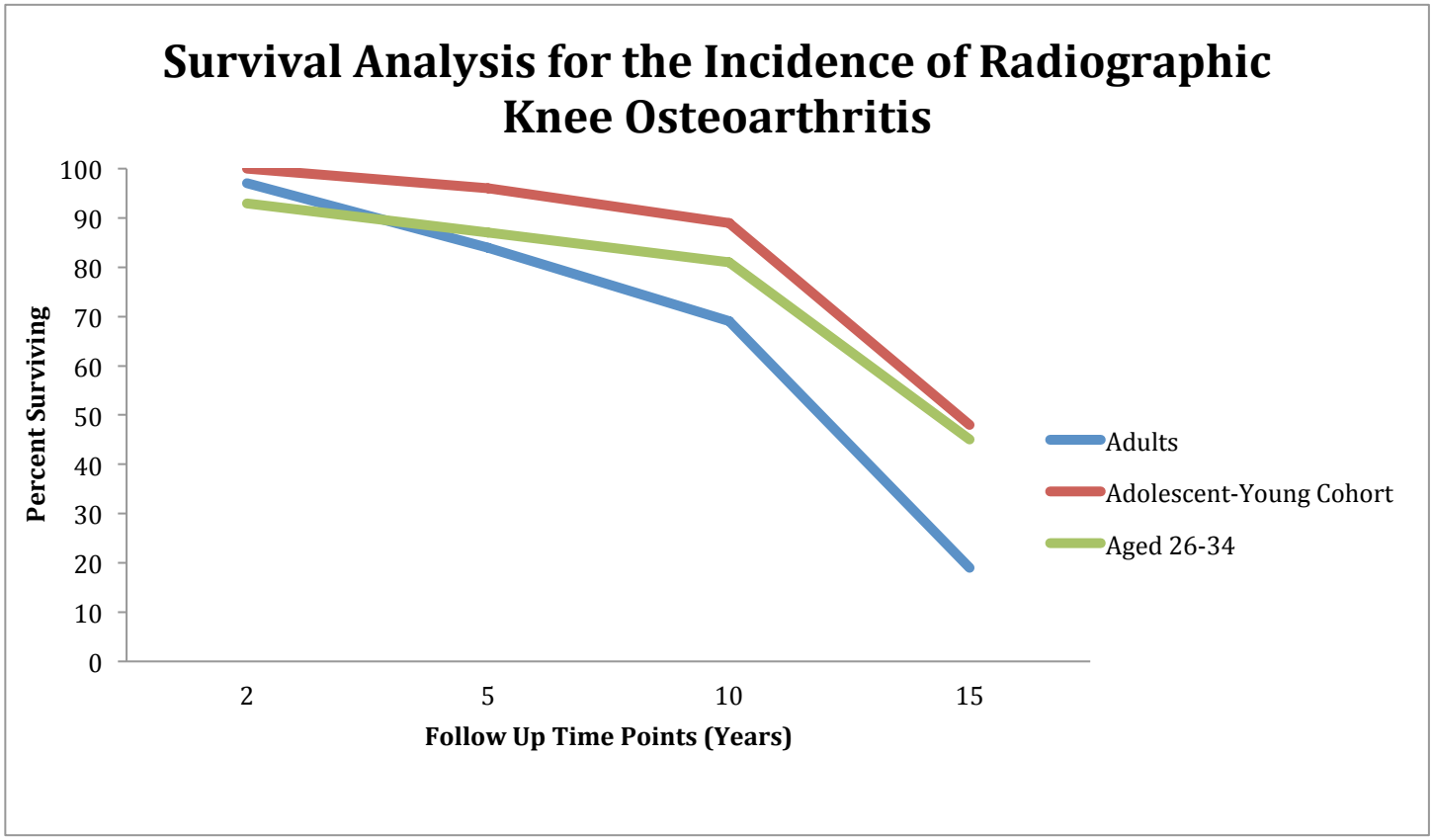

Figure 1: Schema of survival analysis detailing the onset of knee radiographic osteoarthritis. Log-Rank analysis showed no difference between the adult and adolescent survival curves (p-value = 0.4). Chi-squared analysis showed that only at 5 years post-surgery did the difference between adults and the adolescent-young cohort reached statistical significance (p-value = 0.017).

Follow Up Time Points (years)	Adolescent-Young Cohort that developed knee OA (n=112)		Participants aged 26-34years that developed knee OA (n=74)		Adults that developed knee OA (n=32)	
	Number that developed OA	Probability estimate (95%CI)	N that developed OA	Probability estimate (95%CI)	N that developed OA	Probability estimate (95%CI)
2	0	1 (0.96 -1.0)	5	0.93 (0.88-0.98)	1	0.97 (0.82-1.0)
5	4	0.96 (0.91 – 0.99)	4	0.87 (0.83-0.96)	4	0.84 (0.66-0.94)
10	8	0.89 (0.82-0.94)	5	0.81 (0.77-0.92)	5	0.69 (0.50-0.83)
15	46	0.48 (0.39-0.58)	27	0.45 (0.49-0.69)	16	0.19 (0.07-0.37)

Table 3. Kaplan-Meier Survival Analysis for adults, and the adolescent-young and participants aged 26-34 cohort

Discussion

The results presented show that adults who injure their ACL do not have an increased risk of OA incidence at 15 years following knee injury when compared to the adolescent-young population. This study found that whilst adults developed knee OA earlier than the adolescent-young cohort, the difference between the cohorts was no longer significant by 15 years follow up. Further to this the pattern of joint damage for all individuals regardless of age followed a predominantly medial tibiofemoral pattern.

Acute ACL injury is associated with significant changes in bone curvature that is measurable within 3 months of injury leading to reduced congruency of joint surfaces and higher stresses on the articular tissues during activity[8]. Such disruption to articular surfaces and other joint structures such as the meniscus and subchondral bone plate leads to joint instability and is a primary reason why traumatic knee injuries have been widely studied in the adolescent-young cohort due to the strong potential for OA development and earlier onset of functional disability[10].

Our results are supportive of previous studies investigating the relationship between adolescent athletes who rupture their ACL and the incidence of radiographic knee OA. Studies focusing on soccer players found that 12 years after an ACL injury 41%[17] and 51%[12] of men and women exhibited radiographic knee OA respectively. None of these participants were assessed to have OA in their non-injured contralateral knee. A review by Lohmander[19] is in keeping with these results, which suggested that 50% of individuals who suffer a traumatic ACL injury develop OA later in life. Recent data from the Osteoarthritis Initiative also showed that a recent

knee injury, independent of age, was associated with an increased rate of knee OA incidence [2].

However, does this same relationship between knee injury and OA incidence exist amongst mature-aged athletes and older populations? The only other study to have investigated potential differences in OA incidence amongst mature-aged and adolescent athletes was a retrospective, cross-sectional study by Roos et al[16] which found that athletes aged >30years with an isolated ACL injury developed incident radiographic knee OA, on average about 10 years after the initial trauma. This was not significant (p-value = 0.067) to those athletes aged <30years who similarly injured their ACL.

Overall our study produced similar results, that whilst active adults who injured their ACL developed radiographic knee OA initially at a faster rate than their adolescent-young counterparts this difference was no longer apparent at 15 years post-surgery as the adolescent-young cohort produced the same prevalence of knee OA as the adult cohort. Interestingly, studying the histopathology of ACL fibers throughout the aging process has produced results that suggest an older knee would be at a higher risk of incident OA development following injury. Hagawana et al[7] found that intrinsic primary changes in the extracellular matrix, such as an increase in inflammatory cells within the collagen fibers of the ACL increases the fragility of the ligament and by extension may cause ACL mechanical failure. Additionally, analysis of synovial fluid has shown that within days following joint injury there is an increase in turnover of the cartilage proteoglycan aggrecan and type II collagen which may persist for years following injury[9, 11]. These marked cellular changes within the matrix of the ACL

and other joint structures make the ligament vulnerable to injury. Ageing contributes to passive laxity in the ACL ligament[1] with Driban et al[2] establishing that older individuals were at risk of a rapid cascade toward joint failure occurring in less than one year after suffering traumatic injury to their ACL.

As knee trauma represents one of the primary causes of knee OA, when combined with altered ligament morphology due to the natural ageing process theoretically this will place an aged, injured knee at an increased risk of developing incident radiographic knee OA earlier than an adolescent who injures their ACL. One of the primary reasons why our results are not reflective of these studies might be due to a low number of participants in the adult cohort who injured their knee and had radiographs performed at each time point. It was demonstrated that at 5 and 10-years post reconstruction there was a significant difference between adolescents and adults yet this trend didn't continue past this time-point. This study was underpowered and had fewer participants drop out across each follow-up point it would have been interesting to see if this trend continued at 15-years post reconstruction.

An isolated ACL injury is uncommon, so it is also important to note that some individuals in this study suffered concomitant meniscal injuries whilst others sustained further injuries such as ACL graft rupture after reconstruction. Injury to the meniscus was common amongst all three study populations, whilst ACL graft injury was more common amongst the adolescent-young cohort presumably because this cohort is more likely to return to sport following rehabilitation of their initial injury. Individuals that suffer meniscal pathology at the time of ACL injury are at a further increased risk of developing radiographic knee OA later in life than an individual with

an isolated ACL tear[2]. Similarly, it is thought that a second traumatic injury to the knee causing ACL graft rupture may also increase your risk of OA incidence, above that of an individual with a single traumatic event [13].

Limitations

This study highlights the importance of knee injuries in the incidence of knee OA amongst two separate cohorts, but does have a few limitations. The sample size of the adult population was smaller than previous studies investigating similar relationships potentially underpowered the conclusions that can be gleaned from this data. Thus whilst there does appear to be higher rates of OA in adults than the adolescent-young cohort this does not reach statistical significance.

A number of participants did not have radiographs performed at each of the nominated assessment time-points. For this reason there was high number of participants who were not assessed for radiographic changes at each time point throughout this study and could be the reason why at 10- and 15-years post reconstruction the difference between the two cohorts was no longer significant. Having more participants measured at each time-point as well as additional time-points in the future (i.e. measurement at 20 years, 25 years etc) may have produced stronger results.

Magnetic Resonance Images (MRIs) were not collected uniformly at any of the time points in this study. Pre-operative MRIs as well as MRIs at each of the follow up time points would have provided a more accurate description of the cartilage and sub-chondral bone changes that may have occurred throughout the course of this study.

Further while the distinct age cohorts are reasonably well balanced for factors that may predispose to OA including female gender and meniscal injury they are not matched for other factors that can influence OA risk including body mass index and activity levels, which were not controlled for. Given that younger individuals are likely to be more active and participate in high-impact sports when compared to adults it is conceivable that this cohort is at a greater risk of initial injury as well as re-injury following return to sport subsequently increasing their overall risk of radiographic incident knee OA.

Finally, this was a single centered study and all operations conducted by a single surgeon. For this reason the generalizability of these findings to a larger population might be limited.

The results of this study should thus be regarded as hypothesis generating and will require focused, long-term prospective investigations for confirmation of results.

Conclusion

Whilst adults who injure their ACL are at an increased risk of developing knee OA at a faster rate than adolescents, ultimately anyone who injuries their ACL, regardless of age, will develop knee OA within 15 years of injury. However, the rate of incident OA amongst adults who injured their knee in this study is higher than the reported prevalence of approximately 1% of middle-aged adults having radiographic OA due to aging in the absence of other OA risk factors[15]. Injuries amongst the younger, physically active population have so often been the focus of study for the association of injuries and knee OA yet despite the results of this study, injury amongst older adults still needs significant attention. Degradation of the ACL extracellular matrix places makes an aged knee vulnerable to injury and thus may place this population at an increased risk of OA incidence when combined with knee trauma.

It is imperative that the relationship between age, knee injury and OA incidence is studied with a more robust cohort in the future in order to identify whether older adults who injure their knee are at a potentially increased risk of joint instability, disability and ultimately joint failure in a truncated time period. This would lead to prompt recognition of this at-risk population after injury and the production of interventions to delay or prevent the onset of knee OA incident.

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CHAPTER 5

A COMPARISON IN KNEE OSTEOARTHRITIS JOINT DAMAGE PATTERNS AMONGST INDIVIDUALS WITH AN INTACT, COMPLETE AND PARTIAL ANTERIOR CRUCIATE LIGAMENT RUPTURE

This chapter contains the following published peer-reviewed publication:

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AUTHOR CONTRIBUTIONS

V.L. Johnson designed the study question and drafted the manuscript

V.L. Johnson and D.J. Hunter conceived and designed the study, supervised its conduct and take responsibility for the integrity of the work as a whole, from inception to finish.

A. Guermazi, F. Roemer was also involved in the design and conduct of the OAI and FINH studies. Both were also responsible for the scoring and reading of the MRI radiographs.

All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

A COMPARISON IN KNEE OSTEOARTHRITIS JOINT DAMAGE PATTERNS AMONGST INDIVIDUALS WITH AN INTACT, COMPLETE AND PARTIAL ANTERIOR CRUCIATE LIGAMENT RUPTURE

Authors: Victoria L Johnson[1,2], Ali Guermazi[4], Frank W Roemer[4,5] & David J Hunter[1, 6]

Affiliations: [1] Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney, Australia [2] School of Medicine, University of Sydney [4]Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, MA, USA, [5] Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany [6]Rheumatology Department, Royal North Shore Hospital, Sydney, Australia.

Corresponding Author: Victoria L Johnson

Abstract

Aim

The aim of this study was to examine the difference in the pattern of articular damage in persons with either a partial anterior cruciate ligament (ACL) tear; a complete ACL tear or no ACL tear.

Methods

Our study included 600 individuals (Of the 600 individuals, 25 with a partial, 12 with a complete ACL tear and 563 with no ACL tear) from the progression sub-cohort of the Osteoarthritis Initiative. Individuals had a mean age being 61.8years (range 45 – 79years). Chi-square tests were used to compare the location of meniscal pathology, bone marrow lesions (BMLs), and regional cartilage morphology between individuals with a partial or complete ACL tear, as seen on MRI, as well as to a control group of 563 knees.

Results

Individuals with either a complete or partial ACL tear displayed predominantly medial tibiofemoral damage. Individuals with complete ACL tears were more likely to have cartilage lesions in the lateral posterior tibia ($p=0.03$) and the medial anterior femur ($p=0.008$) as well as BMLs in the medial posterior tibia ($p=0.007$). However, no significant difference in meniscal morphology was found in either compartment. Individuals with no history of knee trauma or ACL injury displayed predominantly medial tibiofemoral compartment damage.

Conclusion

Individuals with prevalent ACL disruptions exhibited concomitant osteoarthritic changes in the medial tibiofemoral compartment, as seen on MRI. As the changes in joint tissues were predominantly located in the medial compartment it is thought that these ACL tears may represent a manifestation of the overall disease process rather than the precipitant for OA incidence.

Introduction

Injury to the anterior cruciate ligament (ACL) is common amongst young, active individuals and frequently results in joint instability[1, 2]. The prevalence of knee injuries amongst active adolescents has been estimated to be 0.18%[3], yet the prevalence of incidental ACL tears in the context of established radiographic knee osteoarthritis (OA) has been found to be as high as 35%, many of whom have no recollection of trauma[4]. The etiology and significance of an incidental ACL tear identified in those with knee OA remains unclear. Chondroid metaplasia, collagen fibre disorganization and mucoid degeneration of the ACL extra-cellular matrix may co-exist within the context of osteoarthritis and can occur in individuals without a history of knee trauma[5]. This suggests that the disruption of the ACL may signify degenerative failure of the ligament, as opposed to injury. Regardless of the mechanism, an ACL deficient knee imparts greater translational shear forces on the cartilage and may represent a risk factor for accelerated cartilage destruction[6].

The majority of the literature has focused on comparing the incidence and pattern of radiographic disease in individuals with a history of ACL rupture in adolescence to those individuals who develop radiographic OA but have no history of ACL injury[7-11]. At present time there has been little investigation into whether an incidental ACL tear in individuals with established knee OA alters the pattern of synovial joint damage and no comparison in the location of bone marrow lesions (BMLs), cartilage morphology or meniscal derangement between individuals with either a complete or partial ACL tear. For this reason the risk of OA development and progression in knees with partial ACL tears is unknown. Partial tears may signify that a lower-impact force

was imparted on the knee and thus results in less damage to surrounding structures leading to a different clinical prognosis for future OA development.

The aim of this study was to examine the pattern of articular damage in persons with partial or complete ACL tears by testing the following hypothesis; that complete ACL tears will be associated with increased cartilage loss, meniscal degeneration and display BMLs in the lateral tibiofemoral compartment, consistent with the predominant initial location of the osteochondral injury when compared to individuals with partial ACL tears. An additional aim was to compare the radiographic pattern of damage of those individuals who have prevalent ACL tears to those individuals who have OA but have no ACL tears as seen on MRI to ascertain whether the damage to the ACL leads to different radiographic disease location.

Materials and Methods

Study Design and Participants

The study participants were selected from the Osteoarthritis Initiative (OAI) which is an ongoing ten-year, multi-center, longitudinal, prospective observational cohort study designed to identify biomarkers and risk factors for the development and progression of knee OA. The local institutional review boards approved the study protocol, amendments, and informed consent documentation. The data for this research is available for public access at http://www.oai.ucsf.edu/. The specific datasets used are clinical dataset 0.1.1 and Image Release 0.B.1.

The OAI consists of a progression subcohort and an incidence subcohort. A total of 1,389 participants with radiographic evidence of OA and symptoms of knee OA were recruited for the progression subcohort.

For the purposes of this study, a total of 600 participants were selected from the progression sub cohort. The inclusion criteria required that both of the following criteria be present together in at least one knee at baseline:

1 (OARSI atlas grade ≥1) on *x*-ray[12]. Participants were excluded if they did not meet the criteria of radiographic knee OA defined by a centralized reading of the Kellgren and Lawrence Grading (KLG) of a grade >/equal to 2.

Of these 600 participants, 25 had a partial tear and 12 had complete ACL rupture at baseline as seen on MRI.

Assessment of Joint Injury

History of joint injury was evaluated at the enrolment visit by asking the participants whether they ever injured their knee(s) badly enough to limit their ability to walk for at least two days.

Radiographic Assessment and Knee Selection

Radiographs of both knees were semi-quantitatively scored using Kellgren and Lawrence Grading (KLG)[13], however only one knee per participant was evaluated. The evaluated knee was selected on the evidence of symptomatic radiographic OA. Individuals with knee pain where chosen primarily due to the findings of the Framingham OA study[14] which showed that individuals with symptomatic knees without definite osteophytes have an increased risk of developing radiographic OA compared to knees without symptoms.

In patients with unilateral symptomatic radiographic OA, this knee was chosen for analysis, regardless of radiographic severity. For individuals with bilateral symptomatic radiographic OA, the knee with radiographic appearances that offered the greatest opportunity for detection of progression (KLG score of 2 or 3) was selected. If both knees had KLG scores of 2 or 3 then the knee with the greater extent of the following features was selected: Greater anatomic axis varus angulation, a minimum medial minimum joint space width (JSW) of 2.0 mm, greater grade of medial JSN (grade 1–3), the presence of any medial tibial or femoral osteophyte grade 2 with greater grade than lateral osteophytes or the presence of any medial tibial or femoral osteophyte.

Radiographic images acquired at baseline were read by the OAI central readers for KLG of ≥2 on the postero-anterior (PA) knee radiographs.

MRI Sequence Parameters

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites during the enrollment visit for each of the participants. The following joint structures were assessed: cartilage morphology, subchondral bone marrow lesions (BMLs), meniscal status and meniscal extrusion. The MRI sequences used for each of the joint tissues are described below.

The MOAKS system was used to assess the whole joint for structural changes compatible with knee OA including BMLs, cartilage morphology and meniscal derangement[15]. Inter-rater calibration and reliability testing on a subset of MRI scans was performed for MRI reading quality control. Ongoing surveillance for measurement drift was carried out by a musculoskeletal radiologist (…) by re-reading 5% of the MRIs.

Complete and Partial ACL Tears

Sagittal and coronal intermediate-weighted (IW) 2D Turbo Spin Echo fat suppression views were used to detect the presence of an ACL tear at baseline and were scored as 0= normal, 1 = partial tear and 2 = complete tear. A tear was defined as complete when complete disruption of ACL fibres with ligament discontinuity. Residual straight or tight ACL fibres in at least one-pulse sequence were defined as a partial tear. Signal alterations consistent with mucoid degeneration were excluded.

Intraligamentous hyperintense signal changes without apparent thinning or discontinuity of the ligament consistent with mucoid degeneration of the ACL are not covered by the MOAKS scoring system and were not scored separately. Thus, mucoid degeneration was considered to be part of the "normal" spectrum as the focus was on ligamentous morphologic abnormalities consistent with partial or complete fibre disruption.

Bone Marrow Lesions (BMLs)

A bone marrow lesion was defined as an irregular hyperintense signal in the subchondral bone, proximal to the epiphyseal line, as seen on sagittal IW TSE, time to recovery of 3200ms, time to echo (TE) of 30ms, slice thickness of 3mm, and field of view (FOV) of 160mm. Sagittal Dual Echo in the Steady State (DESS) sequences with slice thickness of 0.7mm, 140mm FOV were used to assist with localization of BMLs.

The BMLs were semi quantitatively evaluated for size and graded at the following locations: medial and lateral patella, medial and lateral trochlea, medial and lateral weight-bearing femur, medial and lateral tibia and subspinous tibia. The MOAKS scores were 0 = none, 1 = <33% of the whole bone volume, 2 = 33-66% of the whole bone volume and 3 = >66% of the whole bone volume. Only grade 3 BMLs in each of the subregions was included in the analysis[15].

Menisci

The menisci were scored using the same sagittal IW TSE FS images as well as the coronal 2D IW TSE images were used to score meniscal integrity. Meniscal damage

was defined according to MOAKS as those menisci that showed disruption of the overall morphology and diffuse hyperintense signal in the body of the meniscus, based on a MOAKS score of >2. Intra-meniscal signal was not considered damage. Meniscal damage was evaluated for in each of the following locations: the anterior horn, body and posterior horn of the medial and lateral menisci.

Cartilage Morphology

Cartilage assessment of both the area size per subregion and percentage of subregion affected by full thickness cartilage loss was graded. The number of subregions with cartilage worsening (i.e., a higher score at 24 months vs. baseline) was defined separately for surface area and thickness. For both scores cartilage worsening was grouped into 4-levels and were defined as, 0 = no change, 1 = <10%, 2 = 10-75% and 3 = >75% of the surface area of that region.

Statistical Analysis

Chi-square tests were performed to examine whether individuals with a complete ACL tear exhibited a specific pattern of meniscal degeneration, BMLs location, bone marrow morphology, and cartilage morphology in the index knee compared with the index knee of those individuals with a partial ACL tear. Significance was set at p-value = 0.05. Statistical analyses were performed using SPSS software (version 22.0, SPSS Inc., Chicago IL.)

Individuals with either a complete or partial ACL tear were then grouped together and these same aforementioned variables were also compared to the index knee of those individuals who did not have an ACL tear.

Results

The demographic characteristics of the overall study sample for participants with a complete, partial or no ACL tear can be seen in Table 1. In total, 356 participants (59% of the total study population) was female with the average age of the participants being 61.8 years with a standard deviation (SD) of 9.4 years and a range of 45 – 79 years of age. The average age of females was 61.7 years (SD of 8.7 years and range 50 – 78 years) and the average age for men being 61.4 years (SD of 9.1 years and range 45 – 79 years). The mean BMI was 30.5kg/m^2 (SD of 5.2). The left knee was picked as the index knee in 279 participants (46%). Of those with a complete ACL tear, a third were female, with an average age of 66 years (SD 7.5 years) and the average age of males being 69 years (SD 6.5 years). The average BMI of females was 32.0 (SD 5.9) and males 29.6 (SD 3.6). On average, 44% those with partial ACL tears were female, with an average age of 71 years (SD 9.5 years) and the average age of males being 65 years (STD 8.6 years). The average BMI of females was 32.4 (SD 7.2) and males 31 (SD 4).

Fifty-nine participants (9.8%) in our study sample did not meet the criteria of radiographic knee OA defined as the Kellgren and Lawrence grade ≥2 by the centralized reading. The eligibility criteria used for the OAI progression subcohort were based on the identification of a definite tibiofemoral osteophyte at each OAI Clinical Center, and some disagreement in radiographic assessment with the adjudicated central reading of KL grades was expected. None of these participants had ACL tears.

A complete tear was present in 12 participants whilst a partial tear was noted in 25 participants. Example radiographs of individuals with either a complete or partial ACL tear are exhibited in Figure 1, whilst Figure 2 provides radiographic examples of BML and meniscal and cartilage pathology. Thirty-five participants with an ACL tear reported a history of substantive previous knee injury, however the exact time when this injury was suffered was not reported. There was no significant difference in meniscal derangement when comparing participants with partial and complete ACL tears (Table 2). Medial meniscal derangement was more common than lateral meniscal derangement, with the majority of damage located in the posterior and anterior horns of the medial meniscus. This pattern of damage was similar amongst both cohorts.

A different pattern of pathology was noted when comparing participants with either a complete or partial ACL tear and those participants who did not exhibit an ACL tear. Participants who did not have an ACL tear did not exhibit pathology as frequently in the anterior or posterior horns of the medial meniscus ($p= 0.003$ and 0.005) or the posterior horn of the lateral meniscus ($p= 0.008$) when compared to those participants who tore their ACL. However, they did have an increased risk of pathology in the central portion of the medial meniscus ($p= 0.001$).

Results for cartilage lesion locations can be seen in Table 3a and cartilage full-thickness lesion sizes in Table 3b. Participants with a complete ACL tear were more likely to have cartilage lesions located in the lateral posterior tibia ($p = 0.03$) and full thickness cartilage lesions in the medial posterior tibia ($p = 0.007$) when compared to

those participants with a partial ACL tear. Those with a partial ACL tear were more likely to have cartilage lesions in the medial anterior femur (p= 0.008).

Significant differences in almost all compartments of the tibia and femur for cartilage lesion locations and lesion sizes were demonstrated when comparing individuals with an ACL tear (combined partial and complete tears) and those without an ACL tear. Significant differences in the location full thickness lesions (as seen in Table 3b) were seen in the lateral posterior tibia (p = 0.01), medial posterior tibia (p = 0.02), central medial tibia (p = 0.001), central lateral tibia (p = 0.004), medial posterior femur (p = 0.004), lateral central femur (p = 0.02) and medial central femur (p =0.001). When considering cartilage lesion sizes (as seen in Table 3a) the subregions that failed to produce significant difference between those with an ACL tear and those without were the lateral central tibia, lateral posterior femur and the medial and lateral anterior femur.

As shown in Table 4, participants with partial ACL tears had more BMLs in the lateral anterior femur (p= 0.038) compared to those with complete ACL tears, whilst those with complete ACL tears had larger BMLs in the medial posterior tibia (p=0.007). BMLs were more frequently seen in the medial patella, medial anterior and subspinous tibias of those individuals without an ACL tear.

	All **n = 600**	**Complete ACL Tear** **n = 12**	**Partial ACL Tear** **n = 25**	**No ACL Tear** **n = 563**
Gender (Female, *n* (%))	356 (59.3)	4 (33.3)	11 (44)	341 (60)
Age (mean, SD) years	61.8 (9.4)	56.9 (8.7)	64.5 (8.8)	61.5 (9.0)
BMI (Mean, SD) kg/m2	30.5 (5.2)	30.2 (4.3)	31.8 (5.6)	30.7 (4.8)
Index knee (left *n*, %))	279 (46.4)	8 (66.7)	11 (44)	260 (46)
Kellgren and Lawrence Grade of index knee (%)				
0	-	-	-	-
1	73 (12.2)	-	2 (8)	71 (12.6)
2	297 (49.5)	5 (41.6)	6 (24)	286 (50.8)
3	225 (37.5)	7 (58.4)	16 (64)	202 (35.9)
4	5 (0.8)	-	1 (4)	4 (0.7)
History of knee injury (yes for study knee *n* (%))	215 (35.8)	12 (100)	23 (92)	180 (31.9%)

Table 1: Study Demographics

	Complete ACL Tear		Partial ACL Tear		No ACL Tear		P- values Complete vs Partial ACL Tear	P- values Tear vs No ACL Tear
	N	**%**	**N**	**%**	**N**	**%**		
Medial Anterior derangement								
No	9	75	23	92	551	98	0.3	**0.003**
Yes	3	25	2	8	12	2		
Medial Body derangement								
No	2	17	11	44	393	70	0.14	**0.001**
Yes	10	83	14	56	170	30		
Medial Posterior derangement								
No	1	8	8	32	307	55	0.22	**0.005**
Yes	11	92	17	68	256	45		
Lateral Anterior derangement								
No	11	92	24	96	539	96	1.0	0.67
Yes	1	8	1	4	22	4		
Lateral Body derangement								
No	11	92	25	100	523	93	0.32	0.5
Yes	1	8	-	0	40	7		
Lateral Posterior derangement								
No	9	75	23	92	539	96	0.3	**0.008**
Yes	3	25	2	8	24	4		

Table 2: Meniscal pathology at baseline for participants with complete, partial and without ACL tears

	Complete ACL Tear (%)				Partial ACL Tear (%)				No ACL Tears (%)				P-Values	
Location	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**Complete vs Partial ACL Tears**	**ACL Tear vs No Tear**
Femur														
- Medial Anterior	75	-	17	8	28	12	60	-	45	12	42	1	**0.008**	0.19
- Lateral Anterior	60	8	32	-	52	4	28	16	63	4	29	4	0.5	0.54
- Medial Posterior	42	25	33	-	40	4	56	-	67	5	28	-	0.16	**0.002**
- Lateral Posterior	92	-	8	-	92	4	4	-	91	8	2	-	1.0	0.13
- Medial Central	16	8	68	8	12	24	72	4	35	16	45	4	0.64	**0.002**
- Lateral Central	67	8	25	-	56	28	16	-	84	12	4	-	0.44	**0.001**
Tibia														
- Medial Anterior	75	-	25	-	60	-	40	-	84	1.7	14	0.3	0.48	**0.025**
- Medial Posterior	50	-	50	-	92	4	4	-	91	8	1	-	0.07	**0.001**
- Lateral Posterior	25	-	75	-	60	12	28	-	65	8	27	-	**0.03**	**0.006**
- Medial Central	34	-	50	16	24	-	68	8	55	2	41	2	0.52	**<0.001**
- Lateral Central	75	-	25	-	72	12	16	-	76	10	14	-	0.52	0.55

Table 3a: Cartilage morphology. Comparison of cartilage surface area between individuals with complete, partial and no ACL tears

	Complete ACL Tear (%)				Partial ACL Tear (%)				No ACL Tears (%)				P-Values	
Location	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**Complete vs Partial ACL Tears**	**ACL Tear vs No Tear**
Femur														
Medial Anterior	92	-	-	8	84	4	16	-	85	5	10	-	0.27	0.31
Lateral Anterior	92	-	8	-	60	8	24	8	76	4	19	1	0.34	0.56
Medial Posterior	66	25	9	-	88	4	8	-	95	3	2	-	0.12	**0.004**
Lateral Posterior	100	-	-	-	100	-	-	-	98	2	-	-	1.0	0.95
Medial Central	33	42	25	-	40	20	40	-	83	8	9	-	0.37	**0.001**
Lateral Central	92	8	-	-	80	12	8	-	97	3	-	-	0.81	**0.02**
Tibia														
Medial Anterior	100	-	-	-	96	4	-	-	96	2	2	1	1.0	0.39
Medial Posterior	66	-	34	-	100	-	-	-	99	-	1	-	**0.007**	**0.02**
Lateral Posterior	66	8	26	-	88	4	8	-	91	4	5	-	0.3	**0.01**
Medial Central	58	17	25	-	56	16	28	-	87	7	6	-	0.99	**0.001**
Lateral Central	75	16	8	-	84	12	4	-	95	3	2	-	0.68	**0.004**

Table 3b: Cartilage morphology. Comparison of cartilage thickness loss between individuals with complete, partial and no ACL tears

Location	BML Size	Complete ACL Tear		Partial ACL Tear		No ACL Tear		P-Values Complete vs Partial Tear	P-Values Tear vs No Tear
		N	%	N	%	N	%		
Lateral Anterior Femur	0	12	100	14	56	400	71	**0.038**	0.53
	1	-	-	6	24	68	12		
	2	-	-	4	16	71	13		
	3	-	-	1	4	24	4		
Medial Anterior Femur	0	10	83	18	72	412	73	1.0	0.92
	1	3	17	6	24	130	23		
	2	-	-	1	4	14	3		
	3	-	-	-	-	7	1		
Lateral Posterior Femur	0	12	100	25	100	543	96	1.0	0.95
	1	-	-	-	-	12	2.8		
	2	-	-	-	-	4	0.7		
	3	-	-	-	-	3	0.5		
Medial Posterior Femur	0	9	75	20	80	472	84	0.83	0.47
	1	2	17	4	16	75	13		
	2	1	8	1	4	13	2.5		
	3	-	-	-	-	3	0.5		
Lateral Patella	0	10	83	11	44	363	64	0.13	0.47
	1	2	17	8	32	97	17		
	2	-	-	5	20	79	14		
	3	-	-	1	4	24	4		
Medial Patella	0	11	92	20	80	358	64	0.35	**0.003**
	1	-	-	4	16	134	24		
	2	1	8	1	4	58	10		
	3	-	-	-	-	13	2		

Lateral Anterior Tibia	0	11	92	25	100	562	99.8	0.32	1.0
	1	1	8	-	-	-	-		
	2	-	-	-	-	1	0.2		
	3	-	-	-	-	-	-		
Medial Anterior Tibia	0	10	83	18	72	482	86	0.63	**0.005**
	1	-	-	2	8	51	10		
	2	2	17	3	12	22	3		
	3	-	-	2	8	8	1		
Lateral Posterior Tibia	0	10	83	24	96	532	94	0.24	0.28
	1	2	17	1	4	24	5		
	2	-	-	-	-	6	1		
	3	-	-	-	-	-	-		
Medial Posterior Tibia	0	8	67	25	100	523	93	**0.007**	0.35
	1	2	17	-	-	21	4		
	2	1	8	-	-	15	2.3		
	3	1	8	-	-	4	0.7		
Subspinous Tibia	0	5	42	4	4	404	72	0.18	**<0.001**
	1	6	50	14	56	125	22		
	2	-	-	5	20	25	5		
	3	1	8	3	12	8	1		

Table 4: Size and location of BMLs in participants with complete and partial ACL tears and in participants without ACL tears.

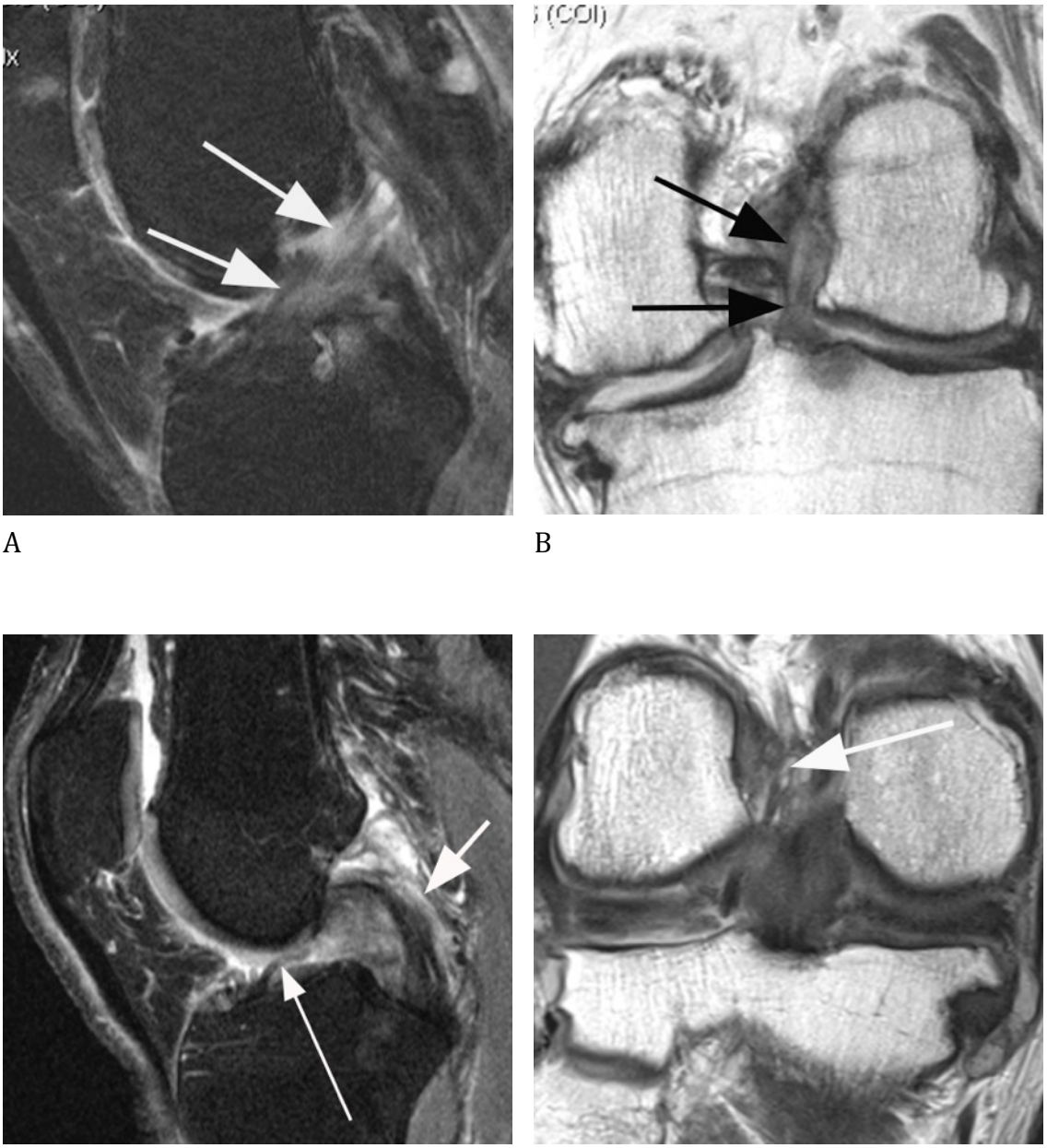
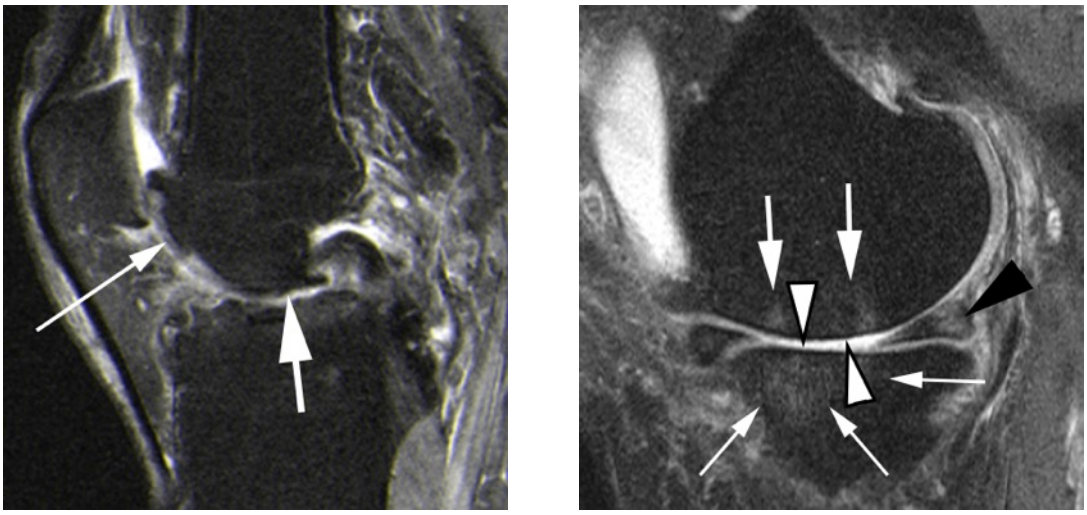
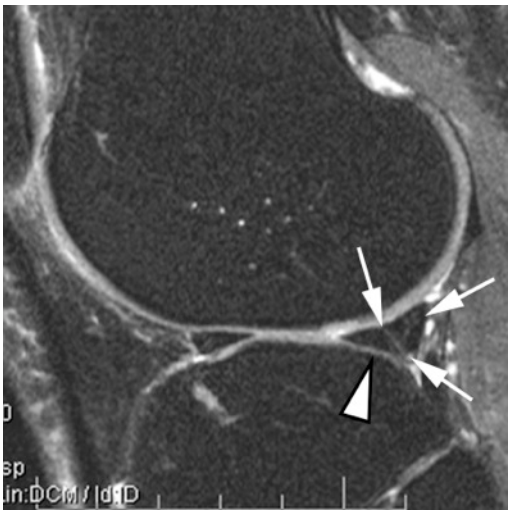


Figure 1. Examples of anterior cruciate ligament (ACL) pathology assessed using the MOAKS grading system. A. Sagittal intermediate-weighted fat-suppressed image shows a thinned ACL with partial fibre disruption but remaining intact component (arrows). B Corresponding coronal intermediate-weighted image confirms these findings and also display marked hyperintensity of remaining fibres (arrows). C. A complete ACL tear is shown in this sagittal image. Only the tibial stump of the ligament can still be discerned (long arrow). Note intact posterior cruciate ligament

(short arrow). D Corresponding coronal image shows proximal femoral remnant of ligament (arrow). There is complete fibre disruption in the intra-ligamentous portion of the ACL.



A. B.



C.

Figure 2. A. Sagittal intermediate-weighted fat suppressed image shows absence of ACL. There is associated full thickness cartilage loss at the medial femoral trochlea centrally (short arrow) and additional superficial cartilage damage further anteriorly of the trochlea (long arrow). B. The same knee as in A. exhibits marked full thickness cartilage loss at the central medial femur and tibia (filled arrowheads). In addition there are associated femoral (thick white arrows) and tibial (thin white arrows) BMLs. Note hyperintensity within the posterior horn of the medial meniscus reflecting mucoid degeneration (black arrowhead). C. Another knee with a partial ACL tear exhibits a complex tear of the posterior horn of the lateral meniscus reaching the

superior, inferior and posterior surfaces (white arrows). In addition there is superficial cartilage loss at the posterior lateral tibial plateau (filled arrowhead), a finding more commonly seen in those knees with prevalent ACL damage compared to those without.

Discussion

Our study is the first to compare structural OA patterns between subjects with complete and partial tears of the ACL on MRI. Overall this study found no clear joint damage pattern differences between those individuals who suffered a complete rupture of their ACL and those who suffered only a partial tear of the ACL fibres. Both complete and partial ACL tears showed predominance for medial tibiofemoral damage with individuals who suffered a complete ACL rupture also exhibiting an increased risk of posterior tibial cartilage damage and BML formation.

A secondary aim of this study was to compare individuals with any type of ACL tear to individuals without an ACL tear. This study demonstrated a clear predisposition to medial tibiofemoral articular damage in persons with OA without an ACL tear seen on MRI.

Recently Eckstein et al[7] quantitatively described medial tibiofemoral cartilage thickening occurring 5 years following ACL rupture. This increase in overall tibiofemoral joint cartilage thickness was also associated with localized cartilage thinning in the posterior subregions of the medial and lateral tibia. Similarly, our study found that individuals with a complete rupture of their ACL suffered significantly larger surface areas of cartilage loss and cartilage lesions in the posterior medial and lateral tibia. To date the precise mechanisms involved in the observed thickening and thinning of joint cartilage following ACL rupture are not well understood. Perhaps the answer lies in the change of knee biomechanics following ACL rupture. Altered tibiofemoral cartilage contact biomechanics have been described following rupture of the ACL with the location of maximum cartilage contact deformation on the tibial plateau becoming more posterior and lateral. This

shift in the area of cartilage contact during weight bearing results in an increase in the magnitude of cartilage contact deformation and causes increased loading of areas that were not conditioned to constant load prior to the loss of the ACL[10, 16, 17]. Adolescent cohorts with ACL-deficient knees have an increased tibial internal rotation and increased posterior translation throughout gait[17]. Thus changes to the biomechanical functioning of the knee secondary to a complete loss of ACL integrity might be the primary reason why complete rupture of the ACL may result in greater cartilage thinning of the posterior tibia when compared to only a partial ACL tear as a partially intact ACL, would still be able to provide some structural support and prevention of translational forces for the injured knee. This suggests that in the long term, individuals who tear their ACL completely may be exposed to more severe knee OA. This will ultimately lead to reduced functionality and greater knee pain. It would be interesting to see if longitudinal studies comparing complete and partial ACL tears support this proposition.

The posterolateral tibia is exposed to strong compression forces during a rupture of the ACL. These forces are predominantly represented on MRI images as posttraumatic BMLs, meniscal derangement and cartilage damage in the lateral tibiofemoral compartment[10, 18-20]. However, none of the individuals with either a complete or partial rupture of their ACL in our study showed BMLs in the lateral posterior tibial region and instead displayed predominance towards medial tibiofemoral damage. Interestingly, Frobell et al[19] found that many of these BMLs that were visualized just following knee injury had resolved 2 years after ACL rupture. As the time from ACL injury to MRI acquisition is not known in our study as well as the fact that the loss of ACL integrity coincides with existing radiographic

knee OA, could possibly explain why the previously documented findings of lateral tibiofemoral damage occurring following ACL rupture were not correlated in our study. Frobell also found that age was significantly associated with BML size. The older an individual was at the time of ACL injury was associated with significantly smaller BMLs when compared to adolescents. The average age of our study participants was 61 years, and yet despite not knowing the age of each individual at the time of injury, this may explain why there was no significant difference in large BML location between individuals with a complete or partial ACL tear.

Finally, a reason for the minimal significant differences observed between individuals with a partial or complete ACL tear could be that regardless of how much the ligament is torn, any amount of force applied to the knee that is strong enough to cause even the smallest amount of fibre damage is enough to cause damage to other adjacent knee structures particularly the subchondral bone underlying the tibial insertion site of the ACL. Thus any injury to the ACL, no matter how significant, carries a similar prognosis for knee joint health.

When comparing individuals with any ACL tear as seen on MRI to those individuals with an intact ACL the predominant pattern of joint damage was not significantly different. That is, that the majority of joint damage was displayed in the medial tibiofemoral compartment. This suggests that the pattern of osteoarthritic damage found amongst all these individuals strongly reflects a pattern consistent with an individual having an injured ACL that occurred within in the context of osteoarthritis and that ligament degeneration may have made the ACL ligament more susceptible to trauma. It is unclear whether an incidental ACL tear identified in an individual with

established knee osteoarthritis reflects disease severity and/or contributes further to progression of cartilage loss in the knee.

There are some limitations in our study. Firstly, this is an exploratory study that utilises a nested case-control within the OAI. Some individuals were selected on the basis of pain and medial joint space width progression. A history of joint injury was established based on participant recall, which introduces an element of recall bias. Further to this the time from reported knee injury to MRI imaging was not recorded in this study. For these reasons it is quite possible that this particular sample will not allow the results of this study to be generalised to a larger community. Further, the number of ACL tears (both partial and complete) is small and this ultimately may be the reason why only minimal significant differences in joint damage between partial and complete ACL injuries were observed. A much larger, more ACL-focused study would need to be performed to better identify relationships between partial and complete tears. Similarly, our sample is much older than a typical ACL injury sample and so any observations made within our study may not be applicable to a younger population.

Conclusion

Overall our study showed minimal significant differences in the joint pattern damage between complete and partial tears of the ACL. Knees with prevalent complete ruptures of the ACL did exhibit greater cartilage thinning of the posterior tibia when compared to joints with only a partial ACL tear. Thus any force applied to the knee that is strong enough to cause injury to the ACL carries a similar prognosis for overall knee joint health. All individuals within this study demonstrated a clear predisposition to medial tibiofemoral articular damage regardless of whether they had an ACL tear as seen on MRI.

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CHAPTER 6

LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE RISK OF SECONDARY MENISCAL INJURY AND BONE MARROW LESIONS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

This chapter contains the following manuscript:

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. Loss of anterior cruciate ligament integrity and the risk of secondary meniscal injury and bone marrow lesions: Data from The Osteoarthritis Initiative.

AUTHOR CONTRIBUTIONS

V.L. Johnson designed the study question and drafted the manuscript

V.L. Johnson and D.J. Hunter conceived and designed the study, supervised its conduct and take responsibility for the integrity of the work as a whole, from inception to finish.

A. Guermazi, F. Roemer was also involved in the design and conduct of the OAI and FINH studies. Both were also responsible for the scoring and reading of the MRI radiographs.

All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

LOSS OF ANTERIOR CRUCIATE LIGAMENT INTEGRITY AND THE RISK OF SECONDARY MENISCAL INJURY AND BONE MARROW LESIONS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

Authors: V.L. Johnson[1,2], A. Guermazi[4], F. W. Roemer[4,5] & D. J. Hunter[1, 6]

Affiliations: [1] Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Australia [2] School of Medicine, University of Sydney [4]Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, MA, USA, [5] Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany [6]Rheumatology Department, Royal North Shore Hospital, Sydney, Australia.

Corresponding Author: Victoria L Johnson

Abstract

Aim

The aim was to determine differences in regard to patterns of meniscal damage (type and location) and bone marrow lesions (BMLs) between subjects with knee OA and prevalent ACL tears and those without tears.

Methods

Six hundred participants (37 with either a complete or partial ACL tear) from the Osteoarthritis Initiative (OAI) study were included. Regional meniscal morphometry measures as well as semi-quantitative scoring of MRI using MRI OA Knee Scores (MOAKS) for the location of meniscal tears and BMLs in index knees were compared between those with and without ACL tears. Chi-square tests were used to compare the prevalence of meniscal damage and BMLs.

Results

37 individuals with an ACL tear (40% female, average age=60.7years, BMI=31.0kg/m^2) displayed increased damage in the anterior regions of the medial meniscus (p-values= 0.002) and the posterior lateral meniscus (p-value=0.03) when compared to individuals without an ACL tear (60% female, average age=61.5years, BMI=30.7 kg/m^2). Horizontal meniscal tears were the most common type of meniscal damage. Individuals with an ACL tear showed large BMLs which were significantly associated with meniscal damage in the anterior medial meniscus and central lateral meniscus (p-values= 0.02 and 0.004 respectively) whilst complex, radial or vertical tears were significant in the medial central and lateral posterior menisci (both p-values 0.002).

Conclusion

Individuals with knee OA and an ACL tear displayed an increased risk of BML incidence with region-specific horizontal medial meniscal tears or medial meniscus partial maceration.

Introduction

Anterior Cruciate Ligament (ACL) tears represent a significant risk factor for the development of radiographic knee osteoarthritis (OA) with the risk of ACL rupture being greatest amongst adolescents who participate in high-risk sports[1] with an annual incidence of approximately 18 injuries per 1000 players in soccer[2]. ACL rupture is strongly associated with the development of knee OA due to subsequent anteroposterior instability of the knee with a substantial percentage of patients beginning to produce radiographic changes consistent with OA and functional disability as early as 10 years after the initial injury[1].

The meniscus acts to distribute loading forces across each of the knee compartments, such that disruption to the meniscus is predictive of longitudinal ipsi-compartmental articular cartilage damage and further structural deterioration within the knee. BMLs signify a consequence of uneven load distribution, as knees with varus mal-alignment are at significant risk for medial tibiofemoral BML formation whilst those with valgus mal-alignment display lateral BMLs[3]. Not only are BMLs associated with pain[3, 4] but they have also been identified as a potential risk factor for the structural progression of OA secondary to their contribution to longitudinal radiographic joint space narrowing and articular cartilage destruction[3]. Whilst meniscal injuries are common findings in patients with acute ACL injuries, recent literature has demonstrated that ACL tears may cause meniscal damage secondary to changes in knee dynamic loading, alignment and subsequent instability due to the absence of a functioning ACL[5, 6]. No literature to date has outlined whether a specific type of meniscal injury is associated with ACL tears – radial, horizontal, vertical or

maceration – or are more likely to produce BMLs and thus increase an individuals risk of further structural damage.

To date the diagnosis of radiographic knee OA (ROA) has been largely based around the presence of radiographic features such as joint space narrowing and the presence of boney osteophytes, however magnetic resonance imaging (MRI) has been shown to have a higher specificity and sensitivity for the assessment of joint morphology[7] and post-traumatic degenerative changes[8].

Therefore, given the importance of the meniscus to joint function, the aim of this study was to determine the relationship between meniscal tears, tear location and BML development in individuals with an ACL tear visualized by MRI at baseline to elucidate which type of tear and its location may identify a knee at greater risk for progression of knee OA following a loss of ACL integrity.

Methods and Materials

Study Design

The study participants were selected from the Osteoarthritis Initiative (OAI) which is an ongoing ten-year, multi-center, longitudinal, prospective observational cohort study designed to identify biomarkers and risk factors for the development and progression of knee OA. 4,796 participants underwent knee MRIs, fixed-flexion knee radiographs, physical examination and questionnaires relating to their knee pain and disability at baseline. Covariants including body mass index, muscle strength, physical activity and injury history were collected in tandem with the outcome assessments.

The study protocol, amendments, and informed consent documentation was reviewed and approved by the Committee on Human Research, who acted as the Institutional Review Board for the University of California, San Francisco and its affiliates (approval number: 10-00532). The data for this research was drawn from the OAI and is available for public access at http://www.oai.ucsf.edu/.

Study Participants

Our study participants were selected from the progression subcohort of the OAI. The inclusion criteria for the progression subcohort of the OAI required that both of the following criteria be present in at least one knee at baseline:

1. Frequent knee symptoms, defined as pain, aching or stiffness on most days of a month during the past year, AND
2. Radiographic evidence of OA defined as definite tibio-femoral osteophytes (OARSI atlas grade >1) on x-ray. Subjects with severe narrowing (OARSI

grade 3 narrowing or bone on bone) in both knees were planned to be excluded. The grading of osteophytes and joint space narrowing was done at each individual OAI enrolment centre.

A total of 600 participants were included for our study purposes. These participants were selected on the basis of previously available data including centralized MRI readings by expert readers for ACL tears and data on chondral morphometry. A breakdown of participant selection can be seen in Figure 1. Of these 600 participants, 37 had either a partial or complete ACL rupture at baseline. Additionally, these participants also exhibited evidence of radiographic knee OA (Kellgren and Lawrence grade >= 2) on x-ray as well as symptoms of knee OA such as pain, stiffness and aching on most days of a month during the past year at baseline.

Radiographic Assessment

Radiography of both knees was performed in all subjects. The radiographs of knees were assessed for their Kellgren and Lawrence Grading (KLG)[9]. Radiographs acquired at baseline were read by the OAI central readers for KLG of ≥2 on the postero-anterior (PA) knee radiographs.

MRI Sequence Parameters

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites during the enrollment visit for each of the participants. The MRI sequences used for each of the joint tissues are described below. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail[10].

The MRI Osteoarthritis Knee Score (MOAKS) system was used to assess the whole joint for structural changes compatible with knee OA including BMLs and meniscal damage[11]. MRI readings were performed by AG and FWR with 14 and 11 years of experience in MRI semi-quantitative assessment, respectively. Scores were entered directly into an electronic web-based database. Inter-rater calibration and reliability-testing on a subset of MRI scans was performed for MRI reading quality control. Subsequently, ongoing surveillance for measurement drift was carried out by AG by re-reading 5% of the MRIs. The intra-rater reliability was kappa = 0.88 and was assessed by reading a sample of 10 knee MRIs twice by the same reader, at least 2 days separated from each other.

ACL Tears

Sagittal and coronal intermediate-weighted (IW) 2D Turbo Spin Echo[12] fat suppression[13] images (time to recovery (TR) of 3200ms, time to echo (TE) of 30ms, slice thickness of 3mm, and field of view (FOV) of 160mm) were used to detect the presence of an ACL tear at baseline and scored on a 0-2 scale (0= normal, 1 = partial tear and 2 = complete tear). A tear was defined as complete when complete disruption of ACL fibres and ligament discontinuity were noted, whilst residual straight and tight ACL fibres in at least one-pulse sequence was defined as a partial tear.

Bone Marrow Lesion

A BML was defined as an irregular hyperintense signal in the subchondral bone, proximal to the epiphyseal line, as seen on sagittal IW TSE. Sagittal Dual Echo in the

Steady State (DESS) sequences (with slice thickness of 0.7mm, 140mm FOV) were used to assist with localization of BMLs. BMLs were scored for size (0-3) at each of nine locations, medial and lateral patella, medial and lateral trochlea, medial and lateral weight-bearing femur, and medial, subspinous and lateral tibia using BLOKS. Only those BMLs with greater than 25% of the surface area adjacent to the subchondral plate were included, thus only BMLs >2 were included in the analysis.

Menisci

Meniscal integrity was scored using the same sagittal IW TSE FS images as well as the coronal 2D IW TSE images. Meniscal damage was defined according to MOAKS as either meniscal tears or substance loss, i.e. partial or complete maceration. Intra-mensical signal was not considered as damage. Meniscal damage was graded at three locations (anterior horn, body and posterior horn) for both the medial and lateral menisci. Morphologic features were scored[14] as:

1. Signal (not extending through meniscal surface).
2. Vertical tear (includes radial and longitudinal tears) – must extend to both the femoral and tibial surfaces
3. Horizontal and radial tear: must extend from the periphery of the meniscus to either a femoral or tibial surface
4. Complex tear: as defined by high signal that extends to both the tibial and femoral surfaces and greater than 3 points on those surfaces
5. Root tear: posterior horn

6. Partial maceration: as defined by loss of morphological substance of the meniscus with or without associated increased signal in the remaining meniscal tissue
7. Complete maceration: no meniscal substance is visible
8. Meniscal hypertrophy: is defined as definite increase in meniscal volume in given subregion when compared to normal

For the purpose of meniscal segmentation the sagittal 3D DESSwe (double echo, steady-state sequence with water excitation) images (slice thickness of 0.7 mm, 16.3ms repetition time, 4.7ms time to echo, 25u flip angle, 160 slices, 140 mm FOV) were used.

Fully automated segmentation of the total cartilage joint surface area was performed for each of the total medial and lateral meniscal volume. MRI-based meniscus thickness measurements were computed from segmentations of the weight-bearing tibiofemoral cartilage plates performed by experienced operators blinded to the time of acquisition and to baseline radiographic readings. Computations for meniscal thickness were then performed.

Statistical Analysis

Chi-square tests were used to determine whether an ACL tear was associated with higher grades of meniscal damage, based on MOAKS, in either the lateral or medial menisci as seen on MRI in each of the medial, central and posterior meniscal regions compared to individuals with no ACL tear at baseline. Following this a comparison was made between the presence of meniscal damage in each of these locations to the

presence of large BMLs. This comparison was analyzed by chi-square tests to evaluate for test significance. The presence of meniscal tears and BML prevalence was further broken down into the type of meniscal tear present (horizontal tear, partial or complete maceration and vertical, radial and complex tears were grouped together). Meniscal volume was compared between the two cohorts using student t-tests. We adjusted the analysis of meniscal volume for confounders including age, BMI, and gender using a linear regression model. Significance was set at $p < 0.05$. Finally, a comparison between medial and lateral meniscal MRI damage was performed using a Fisher's exact t-test in participants who exhibited an ACL tear. Statistical analyses were performed using SPSS software version 7 for Mac.

Results

The demographic characteristics of the overall study sample for participants with an ACL tear and those without can be seen in Table 1. In total, 58 percent (353 of 600 participants) of the total study population was female with the average age of the participants being 61.8 years with an age range of 45 – 79 years. The average age of females was 61.7 years and the average age for men being 61.4 years. The mean BMI was 30.5kg/m^2 (SD of 5.2). The left knee was picked as the index knee in 46% (279 of 600) of participants. Of those with an ACL tear visualised on MRI, 40% were female, with an average age of 60 years (SD 8.7 years) and the average age of males being 69 years (SD 6.5 years). The average BMI of females was 31kg/m^2 (SD 5.6) and males 29.6kg/m^2 (SD 3.6). Of the 37 participants with an ACL tear, 35 (94.6%) reported a history of previous knee injury. Of these 37 participants, 64.9% exhibited a Kellgren-Lawrence Grading (KLG) of ≥ 3 at baseline, compared to 37.5% of participants without an ACL tear having a similar KLG ≥ 3 at baseline.

MRI-detected meniscal damage in at least one portion of the meniscus was present in 21(56.8%) of medial and 1(2.7%) of lateral menisci with 14(37.8%) of knees having both medial and lateral meniscal damage and 1(2.7%) with neither meniscus showing MRI damage as shown in Table 2. There was no statistical significance between medial and lateral meniscal damage (p-value = 0.50).

The prevalence of meniscal damage for each of the anterior, central and posterior regions of both medial and lateral menisci can be seen in Table 3. Additionally, this table also shows whether a tear in each of these regions is associated with BML location. The most frequently damaged region for individuals with an ACL tears was

the central region of the medial meniscus (65%) whilst the posterior region of the medial meniscus was the most frequently damaged region for individuals without an ACL tear (47.2%). Comparison of the two cohorts revealed that damage to the anterior (p-value = 0.002) and posterior regions (p-value = <0.001) of the medial meniscus as well as the posterior region (p-value 0.03) of the lateral meniscus were the only regions to reach statistical significance.

Regardless of the type of meniscal tear sustained on MRI, individuals with an ACL tear and concomitant meniscal damage displayed significantly more BMLs in the central medial meniscus (p-value = 0.008, Table 3) and the posterior lateral meniscus (p-value = 0.03) than those without an ACL tear.

When type of meniscal tear and the subsequent prevalence of large BMLs was compared between individuals with and without an ACL tear (Table 3) it was found that individuals with an ACL tear and a partial maceration of their medial meniscus in either the central (p-value = 0.004) or anterior (p-value = 0.02) portions were significantly associated with large BMLs in the same area as meniscal damage.

Overall meniscal volume did not differ significantly between individuals with an ACL tear and those without and an ACL tear in either the medial or lateral compartments (p-values = 0.88 and 0.24 respectively, Table 4) and remained not significant after con-founders of BMI, age and gender were adjusted for (p-value = 0.30 and 0.95 respectively). Meniscal volumes were not significantly different between the lateral and medial compartment within individuals who demonstrated an ACL tear (p-value = 0.33) as well as those without an ACL tear (p-value = 1.0).

	All **n = 600**	**ACL Tear** **n = 37**	**No ACL Tear** **n = 563**	**P-Values** **ACL Tear vs No ACL Tear**
Gender (Female, *n* (%))	353 (58.9)	15 (40.5)	341 (60)	**0.001**
Age (mean, SD) years	61.8 (9.4)	60.7 (8.7)	61.5 (9.0)	0.67
BMI (Mean, SD) kg/m^2	30.5 (5.2)	31.0 (5.6)	30.7 (4.8)	0.46
Index knee (left *n*, %))	279 (46.4)	19 (51.1)	260 (46)	0.33
Kellgren and Lawrence Grade of index knee (%)				
0	-	-	-	0.18
1	59 (9.8)	2 (5.4)	57 (10.3)	
2	297 (49.5)	11 (29.7)	286 (52)	
3	225 (37.5)	23 (62.2)	202 (36.8)	
4	5 (0.8)	1 (2.7)	4 (0.7)	
History of knee injury (yes for study knee *n* (%))	215 (35.8)	35 (94.6)	180 (31.9)	

Table 1: Study Demographics

Relationship of Medial with Lateral MRI meniscal Damage with an ACL Tear					
		ANY medial MRI damage (medial, central, posterior)			
		Present	Absent	Total	P-Value Fisher's exact t-test
ANY lateral MRI damage (medial, central, posterior)	Present	14 (37.8)	1 (2.7)	15 (40.5)	0.50
	Absent	21 (56.8)	1 (2.7)	22 (59.5)	
	Total	35 (94.6)	2 (5.4)	37	

Table 2: The prevalence of large BMLs stratified by the type of MRI meniscal damage.

The prevalence of large BMLs stratified by the type of MRI meniscal damage						
	Presence of an ACL Tear N = 37	**No presence of an ACL Tear N = 563**	**ACL Tear vs No ACL Tear P-Value**	**ACL Tear and BML Prevalence**	**No ACL Tear and BML Prevalence**	**BML Prevalence ACL Tear vs No ACL Tear P-Value**
Anterior Medial Meniscus [n(%)]						
Horizontal Tear	-	5 (1)	0.56	-	12 (2)	0.37
Complete Maceration	-	-	-	-	-	-
Partial Maceration	5 (14)	9 (1)	1.0	2 (5)	3 (0.5)	**0.02**
Other Tear	-	-	-	-	1 (0.3)	0.8
Overall	5 (14)	14 (2)	**0.002**	2 (5)	16 (3)	0.38
Central Medial Meniscus						
Horizontal Tear	4 (11)	66 (12)	0.87	3 (8)	26 (5)	0.33
Complete Maceration	-	2 (0.5)	0.71	-	-	-
Partial Maceration	18 (49)	100 (18)	1.0	7 (19)	28 (5)	**0.004**
Other Tear	2 (5)	3 (0.5)	**0.002**	-	-	-
Overall	24 (65)	171 (30)	1.0	10 (27)	54 (10)	**0.008**
Posterior Medial Meniscus						
Horizontal Tear	-	161 (29)	**<0.001**	1 (3)	13 (2)	0.88
Complete Maceration	-	1 (0.2)	0.8	-	-	-
Partial Maceration	5 (14)	85 (15)	0.8	2 (5)	11 (2)	0.16
Other Tear	-	19 (3)	0.26	-	3 (0.5)	0.66
Overall	5 (14)	266 (47.2)	1.0	3 (8)	27 (5)	0.37

Anterior Lateral Meniscus [n(%)]						
Horizontal Tear	2 (5)	21 (4)	0.61	2 (5)	14 (2)	0.29
Complete Maceration	-	-	-	-	-	-
Partial Maceration	-	3 (0.5)	0.66	-	1 (0.3)	0.80
Other Tear	-	1 (0.3)	0.80	-	1 (0.3)	0.80
Overall	2 (5)	25 (5)	0.78	2 (5)	16 (3)	0.38
Central Lateral Meniscus						
Horizontal Tear	1 (3)	41 (7)	0.29	2 (5)	-	-
Complete Maceration	-	-	-	-	-	-
Partial Maceration	-	-	-	-	-	-
Other Tear	-	-	-	-	1 (0.3)	-
Overall	1 (3)	41 (7)	0.29	2 (5)	1 (3)	1.0
Posterior Lateral Meniscus						
Horizontal Tear	1 (3)	25 (4)	0.62	-	1 (0.3)	-
Complete Maceration	-	-		-	-	-
Partial Maceration	2 (5)	1 (0.3)	1.0	-	-	-
Other Tear	2 (5)	2 (0.5)	**0.002**	-	-	-
Overall	5 (13)	28 (5)	**0.03**	-	1 (0.3)	-

Table 3: Prevalence of MRI Meniscal Damage and BMLs stratified by the location (medial, anterior or posterior meniscal horns) and by meniscal tear type. A comparison between individuals with and without an ACL tear.

Meniscal Volumes in Individuals with and without an ACL Tear								
	Unadjusted Results					Adjusted Results		
	ACL Tear N = 37	**No ACL Tear N = 563**	**P-Value ACL Tear vs No ACL Tear**	**P-Value Medial vs Lateral Volumes for ACL Tears**	**P-Value Medial vs Lateral Volumes for No ACL Tears**	**Beta Co-Efficient**	**Confidence Interval (95%)**	**P-Value ACL Tear vs No ACL Tear**
Medial Compartment, average mm3 (St Dev)								
Average Meniscal Volume	2535.92 (819)	2569.19 (818)	0.88	0.33	1.0	-0.24	-0.51 – 0.17	0.30
Lateral Compartment, average mm3 (St Dev)								
Average Meniscal Volume	2596.74 (660)	2380 (601)	0.24			-0.01	-0.34 – 0.36	0.95

Table 4: Medial and lateral meniscal volumes at baseline as seen on MRI in both individuals with and without an ACL tear. Included in this table are p-values adjusted for BMI, sex and age

Discussion

Regardless of the presence of an ACL tear, individuals in this study demonstrated predominantly medial tibiofemoral compartment damage with a slight predominance for horizontal tears and partial maceration of the medial meniscus.

Overall, our study found that BMLs were associated with ipsi-compartmental meniscal damage in the medial tibiofemoral compartment amongst individuals with an ACL tear and had a concomitant partial maceration or horizontal meniscal tear. Vertical, radial and complex meniscal tears were identified in the medial meniscal body and posterior portions of the lateral meniscus, however, these tears were not associated with BMLs with not one of these tears being accompanied by an underlying BML regardless of whether an individual had suffered an ACL tear or not. Further, large medial BMLs were more likely to occur in knees that displayed any meniscal damage on MRI than in those knees without any meniscal damage.

The medial meniscus is thought to be pre-disposed to damage, even in the absence of ACL injury, as 70% of the load that passes through the knee joint is transferred through the medial tibiofemoral compartment[15]. When considering knees that have suffered a loss of ACL integrity it has been established that the odds of suffering from a meniscal lesion increases every year post ACL injury with the odds of an injury to the medial meniscus being 2.2 times higher at 2 to 5 years post ACL injury and 5.9 times higher at more than 5 years post ACL injury[5]. Further to this, the type of meniscal tear and tear locations have been found to not only have an influence on extrusion, but also to have a profound effect on cartilage loss, which leads to the progression of symptomatic knee OA[16, 17]. In individuals with OA seen on MRI

but no history of knee injury, it has been found that meniscal maceration, complex tears and degenerative horizontal tears are more frequently displayed in the medial compartment, particularly the central and anterior meniscal horns, and are associated with an increased risk of medial meniscal extrusion[16]. Further to this degenerative meniscal tears have been associated not only with an increased risk in underlying BML development but also a worse long-term prognosis[18]. Current evidence strongly suggests that degenerative meniscal tears generally occur in knees already compromised by changes that may represent incident radiographic OA[1, 19]. Thus in accordance with our study, a horizontal degenerative tear or complete or partial maceration of the meniscus may project region-specific OA disease progression and severity. This is significant as it may represent a possible opportunity for early intervention. Asymptomatic individuals that display MRI meniscal damage represent a cohort who could be targeted for drug interventions that could prevent the incidence of structural damage, such as the occurrence of BMLs and in turn, hopefully, prevent the development of symptomatic OA.

Interestingly, despite differences in the incidence of BMLs between the two cohorts no overall difference in meniscal volumes was observed between the medial and lateral menisci of individuals within each cohort as well as between cohorts. Typically there is thickening of the medial menisci and thinning of the posterolateral menisci amongst individuals with an ACL tear[20, 21]. As the measurement of meniscal volume was an average of the total compartment and was not region specific perhaps this detail in thickening and thinning was lost.

It has been identified that mechanical challenges to cartilage differ between healthy and injured knees as chondrocytes and the cartilage extra-cellular matrix in an ACL-deficient knee are exposed to increased stress. Altered tibiofemoral cartilage contact biomechanics have been described following rupture of the ACL with the location of maximum cartilage contact deformation on the tibial plateaus becoming more posterior and lateral combined with a decrease in the area of contact resulting in an increase in the magnitude of cartilage contact deformation. The posterolateral tibia is exposed to strong compression forces during a rupture of the ACL. These forces are predominantly represented on MRI images as post-traumatic BMLs, posterolateral meniscal and cartilage[20] . These findings are hinted at in our study, as ACL-deficient individuals displayed a small increase in the prevalence of posterolateral meniscal damage. Unfortunately, due to the small sample size of ACL deficit knees in our study, this is only speculative.

This study found no difference in the overall pattern of joint damage between individuals with and without an ACL tear with both cohorts displaying predominantly medial tibiofemoral compartmental damage. Results that did reach statistical significance when comparing these two cohorts (posterior lateral meniscal damage, central medial meniscal damage) are more likely due to a lack of sample power than due to any real observable differences.

Finally, the overall finding of medial tibiofemoral damage amongst individuals with an ACL tear is indifferent to a large number of studies that have previously documented a predominance of lateral tibiofemoral radiographic damage in adolescents who have ruptured their ACL, due mainly to the strong compression

forces applied to the posterolateral tibia during ACL injury[21-23]. Frobell[21] found that two years after the initial ACL injury many of the lateral BMLs that were initially visualized on MRI had resolved. As the time from ACL injury to MRI acquisition is not known in our study as well as the fact that loss of ACL integrity coincided with existing radiographic knee OA, could possibly explain why medial and not lateral BMLs and an overall medial damage pattern predominated in our study individuals.

There are some limitations in our study. The identification of BMLs and MRI meniscal damage occurred using some overlapping MRI sequences which could potentially bias these findings towards a positive association. Additionally, this study utilizes a case-control design of the FNIH subsample of the OAI. As some individuals were selected on the basis of pain and medial joint space width progression we may not be able to make any extrapolations from these findings to the wider community and more longitudinal research is needed. The majority of participants in this study reported a history of knee injury. It is unclear whether injury to the meniscus was sustained at the time of injury or occurred gradually as a result of ACL dysfunction. Finally, the major limitation of this study is that, unfortunately, the number of ACL injuries in this study was small and as such any findings or conclusion made are weakened by the small sample size. Additionally, our sample is of a much older cohort than those who typically injure their ACL, thus with this in mind, this study may not apply to a younger population.

Conclusion

The overall pattern of joint damage exhibited between the two cohorts was not significantly different as regardless of whether an individual had suffered a tear to their ACL or not, both cohorts displayed medial tibiofemoral joint damage.

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CHAPTER 7

THE ASSOCIATION BETWEEN RADIOGRAPHIC ANTERIOR CRUCIATE LIGAMENT TEAR AND JOINT SYMPTOMS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

This chapter contains the following peer-reviewed manuscript:

V.L. Johnson, A Guermazi, F.W. Roemer, D.J. Hunter. The association between radiographic anterior cruciate ligament tear and joint symptoms: Data from The Osteoarthritis Initiative. Under Final Editor Review at *International Journal of Rheumatic Disease*

AUTHOR CONTRIBUTIONS

V.L. Johnson designed the study question and drafted the manuscript

V.L. Johnson and D.J. Hunter conceived and designed the study, supervised its conduct and take responsibility for the integrity of the work as a whole, from inception to finish.

A. Guermazi, F. Roemer was also involved in the design and conduct of the OAI and FINH studies. Both were also responsible for the scoring and reading of the MRI radiographs.

All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

THE ASSOCIATION BETWEEN RADIOGRAPHIC ANTERIOR CRUCIATE LIGAMENT TEAR AND JOINT SYMPTOMS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

Authors: V.L. Johnson[1,2], A. Guermazi[4], F. W. Roemer[4,5] & D. J. Hunter[1, 6]

Affiliations: [1] Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Australia [2] School of Medicine, University of Sydney [4]Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, MA, USA, [5] Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany [6]Rheumatology Department, Royal North Shore Hospital, Sydney, Australia.

Corresponding Author: Victoria L Johnson

Abstract

Introduction

Symptomatic osteoarthritis (OA) is defined as the presence of the OA radiographic features in combination with knee symptoms. Pain has not been shown to correlate meaningfully to radiographic severity. We aimed to determine the relationship between a tear of the anterior cruciate ligament (ACL) with knee symptoms and radiographic OA.

Methods

A within-person, between-knee cross-sectional study of 37 participants from the Osteoarthritis Initiative (OAI) with a complete or partial ACL tear detected on MRI in one knee (index knee) were included. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS) and radiographs of both knees, one with an ACL tear and one without (control knee) were scored for OA severity (Kellgren-Lawrence Grading) and symptoms. A generalised estimating equation with linear regression was used to compare symptom scores within-individuals as well as to radiographic severity.

Results

37 individuals (40% female, average age=60.7years, BMI=31.0kg/m^2) reported no difference in knee symptoms (WOMAC pain OR=1.92 95%CI 0.699–5.248, p-value=0.21, KOOS symptoms OR=2.12 95%CI 0.740–6.065, p-value=0.09), stiffness (OR=1.67 95%CI 0.653–5.583, p-value=0.35) or functional disability (OR=1.97 95%CI 0.515–7.508, p-value=0.32) in the knee that exhibited an ACL tear compared to the control knee. Only knee function and disability (WOMAC Disability OR=1.12

95% CI 1.003–1.249, p-value=0.04) was associated with radiographic severity between index and control knees.

Conclusion

Individuals did not report an increase in knee pain, stiffness or disability in their ACL deficient knee. Only disability was associated with worsening severity of radiographic OA in ACL deficient knees.

Introduction

The characteristic symptom of knee osteoarthritis (OA) is pain which contributes greatly to an individual's functional decline and reduced quality of life. Furthermore, persistent knee pain has been cited as the predominant reason why individuals pursue medical attention[1, 2]. It has been estimated that approximately 27 million adults in the United States of America have clinical knee OA as defined on the basis of both physical findings and symptoms, with symptomatic knee OA being defined as the presence of both knee symptoms and the characteristic radiographic features of OA[3]. The etiology of knee pain is multifactorial and the degree to which structural pathology contributes to each individual's pain experience remains controversial. To date only a weak correlation between the severity of radiographic OA and patient reported symptoms has been demonstrated[4, 5]. However, whilst symptoms may not correlate to radiographic severity it has been well documented that symptoms such as pain and stiffness have clear contributions to functional limitations in knee OA[6, 7].

Tearing of the anterior cruciate ligament (ACL) is a common and serious knee injury amongst adolescents and young adults. Individuals who suffer a knee injury involving the ACL are at an increased risk of developing knee OA irrespective of surgical or conservative treatment[8]. Loss of ACL integrity produces increased translational shear forces such as increased tibial internal rotation subsequently causing altered cartilage loading patterns culminating in increased cartilage destruction and incident knee OA[9]. Consequently, a loss of ACL integrity within an already damaged joint may lead to further disease progression, increased disease severity and disease of the whole joint, rather than a compartment specific damage pattern[10].

The investigation of knee symptoms secondary to an injury to the ACL has largely focused around adolescents and young adults who have suffered an acute ACL tear. Data from the KANON trial showed that 5 years after suffering an ACL injury individuals reported an increase in joint pain, symptoms and poor physical functioning regardless of treatment option[11]. Similarly Lohmander et al[12] reported a higher degree of pain and disability amongst soccer players up to 12 years post ACL injury. There is currently no data to suggest whether these knee symptoms can be extrapolated to an elderly cohort with a similar loss of ACL integrity.

Clinicians often rely on radiographs to confirm a diagnosis and for directing treatment of knee OA and yet currently the presence of radiographic OA changes does not allow them to predict the presence of knee symptoms nor allow for estimation of disease progression within individual patients. Because not all individuals with radiographic OA have concomitant symptoms it is difficult for clinicians to identify, which individuals are at greatest risk of disease progression as the risk factors for structural disease and symptomatic disease may not be one and the same. Thus whilst finding an association between symptoms and radiographic disease is important in knee OA, this association is even more important in knees that have sustained an injury. Individuals with a history of knee injury are at an increased risk of more severe disease in a truncated time course and are likely to suffer worsening functional disability.

With this in mind, the purpose of our study was to determine the relationship between a tear of the anterior cruciate ligament (ACL) with radiographic knee OA and the knee symptoms by performing a within-person, between knee comparison of

radiographs, WOMAC and KOOS scores amongst individuals with an ACL tear in one knee and an intact ACL in the other knee.

Methods

Study Design

The study participants were selected from the Osteoarthritis Initiative (OAI) which is an ongoing ten-year, multi-center, longitudinal, prospective observational cohort study. The OAI is designed to identify biomarkers and risk factors for the development and progression of knee OA. 4,796 participants underwent knee MRIs, fixed-flexion knee radiographs, physical examination and questionnaires relating to their knee pain and disability at baseline. Covariates including body mass index, muscle strength, physical activity and injury history were collected at the same time as the outcome assessments.

The local institutional review boards reviewed and approved the study protocol, amendments, and informed consent documentation. The data for our research was drawn from the OAI and is available for public access at http://www.oai.ucsf.edu/.

Study Participants

Our study participants were selected from the progression subcohort of the OAI. The inclusion criteria for the progression subcohort of the OAI required that both of the following criteria be present in at least one knee at baseline:

3. Frequent knee symptoms, defined as pain, aching or stiffness on most days of a month during the past year, AND
4. Radiographic evidence of OA defined as definite tibio-femoral osteophytes (OARSI atlas grade >1) on x-ray. Subjects with severe narrowing (OARSI grade 3 narrowing or bone on bone) in both knees were planned to be

excluded. The grading of osteophytes and joint space narrowing was done at each individual OAI enrolment centre.

A total of 37 participants from the Foundation for the National Institutes of Health (FNIH) sub-sample of the OAI were included for our study, which comprises a within-person, between knee comparison of knee symptoms and radiographic knee OA. These participants exhibited either a partial or complete ACL tear in one knee (the index knee) at baseline and an intact ACL in the other knee (the control knee). Study participants displayed evidence of radiographic knee OA (Kellgren and Lawrence grade >= 2) on x-ray in the index knee as well as symptoms of knee OA such as pain, stiffness and aching on most days of a month during the past year at baseline.

Radiographic Assessment

Radiography of both knees was performed in all subjects. The radiographs of knees at baseline were assessed by the OAI central readers for their Kellgren and Lawrence Grading (KLG)[13] on the postero-anterior[4] knee radiographs.

MRI Sequence Parameters

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites during the enrollment visit for each of the participants. The MRI sequences used for each of the joint tissues are described below. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail[14].

The MRI Osteoarthritis Knee Score (MOAKS) system was used to assess the whole joint for structural changes compatible with knee OA including BMLs and meniscal damage[15]. MRI readings were performed by AG and FWR with 14 and 12 years of experience in MRI semi-quantitative assessment of knee OA features, respectively. Scores were entered directly into an electronic web-based database. Inter-rater calibration and reliability-testing on a subset of MRI scans was performed for MRI reading quality control. Subsequently, ongoing surveillance for measurement drift was carried out by AG by re-reading 5% of the MRIs.

ACL Tears

Sagittal and coronal intermediate-weighted (IW) 2D Turbo Spin Echo[16] fat suppressed[17] images (time to recovery (TR) of 3200ms, time to echo (TE) of 30ms, slice thickness of 3mm, and field of view (FOV) of 160mm) were used to detect the presence of an ACL tear at baseline and scored on a 0-2 scale (0= normal, 1 = partial tear and 2 = complete tear). A tear was defined as complete when complete disruption of ACL fibres and ligament discontinuity were noted, whilst residual straight and tight ACL fibres in at least one-pulse sequence was defined as a partial tear.

History of Knee Injury

At baseline, study staff asked participants: “Have you ever injured your right knee badly enough to limit your ability to walk for at least 2 days?” A similar question was asked for the left knee. We defined a history of injury as anyone who reported a history of injury at the baseline OAI visit.

Knee Pain, Stiffness and Physical Functioning Evaluation

Knee-specific pain, knee stiffness and physical functioning were assessed at baseline using the well-validated Western Ontario and McMaster Universities Osteoarthritis index (WOMAC)[18] as well as the Knee Injured and Osteoarthritis Outcome Score (KOOS).

The WOMAC pain score is divided into 3 categories – pain, stiffness and functioning. Each of these scores is assessed using a 5-point Likert scale. Pain when performing different activities (e.g. walking, climbing stairs, lying down) is evaluated over the past 7 days using and are assessed on the Likert scale as 0 = no pain and 4 = severe pain which were summed for a total WOMAC pain score (range 0-20).

Stiffness is assessed by asking if individuals ever feel knee stiffness after first waking or later in the day, which were summed for a total WOMAC stiffness score (range 0-8).

Physical functioning consists of 17 questions and focuses on an individual's ability to perform activities of daily living (e.g. stair use, rising from sitting, getting in and out of a car, shopping, walking), which were summed for a total WOMAC physical functioning score (range 0-68).

The KOOS score is divided into 5 categories including knee pain, symptoms, activities of daily living, sport and recreation and overall quality of life. For the purpose of this study the knee pain and symptoms sub-scales were used. When answering the KOOS questions individuals are asked to consider whether each of these symptoms occurred in the previous week. Each question is scored in the range

of 0 (no problems) to 4 (extreme problems). The scores are transformed using a 0–100 scale, with zero representing extreme problems and 100 representing no problems. The KOOS score was included in this study because it asks very specific questions regarding the functioning of their knees under the symptoms subscale. For this reason each of the individual KOOS symptoms questions were individually analysed. These questions ask participants whether they have experienced any of the following within the past week;

1. Knee catching or hang-up
2. Knee clicking or grinding
3. Knee swelling
4. Difficulty with knee bending
5. Difficulty with knee straightening

These are questions that are not covered in the WOMAC questionnaire.

Given that there is significant overlap in the questions covered by both the WOMAC and KOOS pain and stiffness scores, analysis of each of the individual KOOS pain questions and inclusion of the overall KOOS stiffness score was not performed.

Statistical Analysis

Scores for each of the questions in each of the domains in the WOMAC (pain, stiffness and functioning) and KOOS (pain, symptoms, and the individual scores for each of the KOOS knees symptoms questions) were averaged to produce a total score. Total as well as individual domain scores from both the WOMAC and KOOS questionnaires were then compared between knees that had an ACL tear (index knee) to those that did not have an ACL tear (control knee). Following this, WOMAC and

KOOS scores were then compared to KLG scores to assess whether radiographic disease correlated with patient-reported symptoms, with radiographic knee OA being defined as KLG greater than or equal to 2. Both of these comparisons were performed using generalized estimating equation. Data is presented as both p-values and odds ratios with 95% confidence intervals calculated. Statistical significance was set at 0.05.

Results

The demographic characteristics of the overall study sample for individuals with a unilateral ACL tear can be seen in Table 1. In total, 40.5% (15 of 37 participants) of the total study population was female with the average age of the participants being 60.7 years with a standard deviation (SD) of 8.7. The mean BMI was 31kg/m^2 (SD of 5.6). The left knee was picked as the index knee in 51.1% (19 of 37) of participants. In total 35 of the 37 participants (94.6%) reported a history of previous knee injury and 24 participants (64.9%) exhibited a Kellgren-Lawrence Grading (KLG) of ≥ 3 at baseline in their index knee, compared to 19 participants (54%) of knees without an ACL tear having a similar KLG ≥ 3 at baseline (p-value = 0.04). Specifically, 11 knees with ACL tears had a KLG of 2 (29.7%), 22 with a KLG of 3 (62.2%) and a single knee had a KLG of 1 (2.7%). For knees that did not have an ACL tear, 14 had a KLG of 2 (35.1%), 18 had a KLG of 3 (51.3%) and again a single knee had a KLG of 4 (2.7%). Ten individuals had the same KLG in both their index and control knees (27%).

Individuals did not report a difference in the severity of symptoms in the knees that contained an ACL tear in comparison to the knee that did not contain an ACL tear (KOOS symptoms score OR 2.12, p-value = 0.09, WOMAC pain score OR 1.92, p-value = 0.21) as seen in Table 2. The index knee was reportedly more likely to exhibit symptoms of knee swelling (OR 1.91), catching (OR 2.13), clicking (OR 2.12), pain with knee straightening (OR 2.05) and functional disability (OR 1.97) but none of these approached statistical significance. Furthermore, there was no significant difference identified between radiographic severity and any of these scores (knee swelling OR 1.36 p-value = 0.07, knee clicking OR 1.0, p-value = 0.9, knee catching

OR 1.58, p-value = 0.33, knee straightening OR 0.56, p-value = 0.28) as outlined in Table 3.

In knees that exhibited an ACL tear, the only symptom that was significantly associated with radiographic severity was reduced knee function and disability (WOMAC Disability score OR 1.12, p-value 0.04).

Study Demographics			
	Knee with ACL Tear N = 37	**Knee with No ACL Tear N = 37**	**P-Value**
Age (mean, SD) years	60.7 (8.7)		
Gender (Female, *n* (%))	15 (40.5)		
BMI (Mean, SD) kg/m^2	31 (5.6)		
Index knee (left *n*, %))	19 (51.1)	18 (48.9)	
Kellgren and Lawrence Grading for Index Knee (%)			
0	-	-	
1	2 (5.4)	4 (10.8)	
2	11 (29.7)	14 (35.1)	**0.04**
3	23 (62.2)	18 (51.3)	
4	1 (2.7)	1 (2.7)	
Participants with same Kellgren Lawrence Grading in both the index and control knees (%)	10 (27)		
History of knee injury to the index knee (*n* (%))	35 (94.6)		

Table 1: Study Demographic

Comparison of WOMAC and KOOS Average Scores between Knees with an ACL Tear and those Without an ACL Tear				
Scale (Score Range)	**Average Score for Knees with an ACL Tear (SD)**	**Average Score for Knees without an ACL Tear (SD)**	**P-Value**	**Odds Ratio (95% CI)**
WOMAC Pain (0 – 20)	2.5 (3.2)	2.0 (3.5)	0.21	1.92 (0.699 – 5.248)
WOMAC Stiffness (0 – 8)	1.8 (1.6)	1.3 (1.7)	0.35	1.67 (0.668 – 4.896)
WOMAC Disability (0 – 68)	8.5 (10.9)	6.0 (9.1)	0.32	1.97 (0.515 – 7.508)
KOOS Pain Score (0 – 100)	87.2 (16.9)	84.1 (18.0)	0.09	2.12 (0.740 – 6.065)
KOOS Overall Symptoms Score (0 – 100)	81.9 (16.8)	88.3 (13.5)	0.30	2.12 (0.606 – 7.429)
KOOS Catching (0 – 4)	0.6 (0.8)	0.3 (0.7)	0.07	2.13 (0.944 – 4.820)
KOOS Clicking or Grinding (0 – 4)	1.0 (1.2)	0.8 (1.1)	0.16	2.12 (0.737 – 6.105)
KOOS Swelling (0 – 4)	0.92 (1.4)	0.46 (1.0)	0.24	1.91 (0.653 – 5.583)
KOOS Bending (0 – 4)	0.6 (1.0)	0.27 (0.8)	0.19	1.89 (0.682 – 5.248)
KOOS Straightening (0 – 4)	0.38 (0.8)	0.41 (0.97)	0.22	2.05 (0.699 – 5.988)

Table 2: Comparison of WOMAC and KOOS Average Scores between Knees with an ACL Tear and those Without an ACL Tear using a GEE.

Comparison of Radiographic Severity (KLG) with WOMAC and KOOS Scores for Knees with an ACL Tear			
Scale	**Average Score for Knees with an ACL Tear**	**P-Value**	**Odds Ratio (95% CI)**
WOMAC Pain (0 – 20)	2.5 (3.2)	0.31	1.12 (0.877 – 1.1440)
WOMAC Stiffness (0 – 8)	1.8 (1.6)	0.15	1.53 (0.852 – 2.761)
WOMAC Disability (0 – 68)	8.5 (10.9)	**0.04**	1.12 (1.003 – 1.249)
KOOS Pain Score (0 – 100)	87.2 (16.9)	0.92	1.09 (0.977 – 1.026)
KOOS Overall Symptoms Score (0 – 100)	81.9 (16.8)	0.76	1.005 (0.972 – 1.040)
KOOS Catching (0 – 4)	0.6 (0.8)	0.33	1.58 (0.627 – 3.959)
KOOS Clicking or Grinding (0 – 4)	1.0 (1.2)	0.90	0.993 (0.803 – 1.260)
KOOS Swelling (0 – 4)	0.92 (1.4)	0.07	1.36 (0.965 – 1.926)
KOOS Bending (0 – 4)	0.6 (1.0)	0.29	1.59 (0.677 – 3.753)
KOOS Straightening (0 – 4)	0.38 (0.8)	0.28	0.56 (0.300 – 1.055)

Table 3: Comparison of KLG and WOMAC and KOOS Average Scores for Knees with an ACL Tear

Discussion

Our study investigated radiographic OA and symptoms using WOMAC and KOOS scores of 37 individuals who exhibited an ACL tear in one knee (the index knee) and an intact ACL in the contralateral knee (the control knee) detected on MRI. There was no significant difference between the two knees for any of the 3 WOMAC domains of pain, stiffness or disability or for either of the KOOS domains of pain or symptoms.

Further breakdown of this score showed that whilst participants may have been more likely to report symptoms of catching, clicking, swelling and grinding within their ACL deficient knee as well as swelling, clicking and grinding, symptoms these scores did not approach statistical significance when compared to reported symptoms from the control knee which did not contain an ACL tear. This is surprising given that a loss of ACL integrity has been shown to cause increased tibial posterior translation and internal rotation. Furthermore, this increase in sheer stress on the tibial plateau has been shown to result in changes in both the dynamic and static loading patterns in an ACL deficit knee[19]. These changes in knee kinematics means that previously unloaded chondrocytes and extra-cellular matrix are being subjected to increased stress ultimately resulting in thinning of the posterolateral tibial cartilage and an increase in the incidence of subchondral bone marrow lesions in a similar area[17, 20]. Thus it would be expected that these changes in knee kinematics would result in worsening of knee symptoms and disability. A possible reason why there was no significant difference in symptoms between the two knees is that radiographic knee OA was present in both the control and index knees, thus individuals reported symptoms and disability in both knees even though the underlying pathology of the OA and location of the joint damage may have been different.

Given these altered knee kinematics secondary to a loss of ACL integrity, it is unsurprising that increasing joint-space narrowing on knee radiographs correlates positively with reduced overall knee function and disability which is likely secondary to mechanical obstruction from osteophytes on the joint margins.

These findings further underline the fact that the structural radiographic correlates of OA such as joint-space narrowing, osteophyte formation, and subchondral bone sclerosis may not correlate significantly to the overall pain experience of an individual, particularly at mild to moderate radiographic disease. As radiographs are not accurate in providing insight into which of the structural pathologies are contributing significantly to an individual's knee pain perhaps there is a role for routine MR imaging of individuals who are suspected of having knee OA. MRI has been found to be sensitive in detecting disease incident and several structural changes such as bone marrow lesions, synovitis and effusion have been found to correlate well with reported knee pain[21].

Our study had limitations. Firstly, this is an exploratory study that utilises a nested case-control design of the FNIH subsample of the OAI and as such the results of our study may not be extrapolated to a larger community. Further, the number of ACL tears is small and the time from initial knee injury to imaging by MRI was not measured. Similarly, it is important to note that this sample is much older than a typical ACL injury sample and so any assertions or assumptions made within our study may not be applicable to a younger population. Finally, our study was

comparing knees within individuals. For this reason there might be recall bias regarding symptoms and pain.

Conclusion

Individuals with an ACL deficient knee did not report significantly increased levels of symptoms, stiffness or functional disability despite having moderate to severe radiographic knee OA. ACL deficient knees have an increased adduction moment in the stance phase of gait and this has subsequently been shown on MRI to produce posterolateral joint damage. Our study suggests that altered knee kinematics secondary to a loss of a functional ACL may contribute to worsening radiographic severity in individuals with already established knee OA.

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CHAPTER 8

THESIS SUMMARY

Thesis Summary and Clinical Implications

It has been extensively documented that traumatic injury to the ACL in adolescence confers a significantly increased risk of incident knee OA, often occurring as early as 10 years after the initial injury. An acute ACL injury has been associated with significant changes in bone curvature that reduces the congruency of joint surfaces and imparts higher stresses on the articular tissues during knee movement. Such disruption to the articular surfaces and joint tissues leads to joint instability and is a primary reason why traumatic knee injuries have been widely studied in adolescents due to the strong potential for OA development and earlier onset of functional disability.

Yet, it is currently unclear whether this relationship between a loss of ACL integrity and radiographic knee OA could be extrapolated to include an older adult cohort. More importantly, it has not been clear whether age at the time of injury, degree of ACL injury, and extent of damage to surrounding joint structures confer an increase in the risk of knee OA development. As knee trauma represents one of the primary causes of secondary knee OA, when combined with altered ligament morphology due to the natural ageing process this should theoretically place an aged, injured knee at an increased risk of developing incident radiographic knee OA earlier and more severely than an adolescent who injures their ACL.

This thesis further highlights the importance of the ACL in knee functioning and that the loss of ligamentous integrity can potentially lead to worsening knee symptoms such as swelling, grinding and clicking which ultimately can lead to reduced quality of life and an increase in overall morbidity (Chapter 7).

When looking directly at the relationship between a loss of ACL integrity and the incidence of radiographic knee OA, only those individuals with a reported history of knee injury had a significantly increased risk of incident radiographic knee OA. Aged knees that have not undergone previous trauma but have a loss of ACL integrity secondary to other causes, such as age-related degeneration or OA disease progression involving the destruction of the ligament, are not predisposed to incident radiographic knee OA (Chapter 3). It still remains unclear whether an incidental ACL tear identified in an individual with established knee OA reflects disease severity and/or contributes further to progression of cartilage loss at the knee.

Investigation of age at the time of injury revealed that active adults aged >35 years who injured their ACL were found to be at any increased risk of developing radiographic knee OA initially at a faster rate than their adolescent counterparts 5 to 10 years post injury (Chapter 4). This finding was in accordance with Driban et al[1] who established that older individuals were at risk of a rapid cascade toward joint failure occurring in less than one year after suffering traumatic injury to their ACL thus highlighting the significance of injury to an aged knee.

Interestingly, the degree of injury to the ACL may not significantly alter an individual's risk of radiographic knee OA nor influence the pattern of the joint structural damage. Investigation of radiographic joint damage patterns amongst individuals with either a partial ACL or complete ACL rupture revealed that any force applied to the knee that is large enough to cause any degree of fiber straining or tearing increases an individuals risk of knee OA. Regardless of the severity of ACL fiber disruption there was no significant difference in the overall pattern of structural

joint damage with individuals displaying predominantly medial tibiofemoral compartment damage (Chapter 6). A complete ACL tear in those with established knee OA may result from different mechanisms than the acute ACL tear in younger persons, especially since many have no recollection of a significant knee injury which would have resulted in an ACL tear. It may result from repetitive minor trauma which eventually attenuates the ACL so that it tears. Thus regardless of the mechanism for ACL tear, ACL deficient knees are more unstable, and the translational shear force on the cartilage has been speculated as a risk factor for accelerated cartilage degeneration. Ultimately, this illustrates the importance of the ACL to the structural integrity of the knee such that any amount of injury or strain carries a similar prognosis for overall knee joint health. Clinically,

Regardless of age or the degree of injury to the ACL, all studies in this thesis illustrated joint damage primarily in the medial tibiofemoral compartment. Further investigation of the adjacent joint structures associated with ACL injury showed that injury to this ligament was associated with predominance for horizontal or partial maceration of the medial meniscus in the central and anterior portions that were also significantly associated with large bone marrow lesions (Chapter 6). The significance of this finding is underscored by the fact that medial meniscal maceration and degenerative meniscal tears have been found not only to have an influence on meniscal extrusion, but also to have a profound effect on cartilage loss and as such may project region-specific OA disease progression and severity.

ACL tearing, in particular complete rupture of the ACL, was also associated with increased incidence of posterolateral meniscal damage including vertical, complex or

radial lateral meniscal tears as well as anterior tibial cartilage thinning. These meniscal lesions did not, however, translate into an increased risk of bone marrow lesion formation in a manner similar to the medial compartment. The occurrence of posterolateral damage is likely secondary to the increased tibial internal rotation and increased posterior translation of the knee throughout gait in the absence of a functioning ACL. The clinical importance of this finding is that complex and radial meniscal tears have been previously associated with worse OA knee symptoms and usually require surgical intervention.

Whilst this thesis has focused on the radiographic consequences of ACL injury, the primary focus of patients is their risk of worsening knee symptoms with OA incidence and progression. Individuals with an ACL tear reported an increased prevalence of knee swelling, grinding, catching and stiffness in the context of moderate to severe radiographic knee OA. Severe radiographic disease was significantly associated with knee bending and reduced knee functionality.

Injuries amongst the younger, physically active population have so often been the focus of study for the association of injuries and knee OA yet despite the results of this thesis, injury amongst older adults still needs significant attention. Degradation of the ACL extracellular matrix places makes an aged knee vulnerable to injury and thus may place this population at an increased risk of OA incidence and ultimately may progress to total joint failure at a faster rate.

If ACL tears in an elderly cohort are in fact due to a different pathogenesis and therefore do not produce the same structural damage as an adolescent who tears their

ACL in a high-impact sporting injury, then ultimately this cohort will suffer different patterns of functional disability and pain. For this reason clinicians should approach injuries amongst the elderly with a different approach to adolescents who injure their knee. These individuals have a further increased risk of early incident knee OA above that of adolescents with the disease potentially progressing at a faster rate and involving the entire knee joint, not just a single compartment.

Adolescents who injure their knee often opt for surgery in order to return to sport, however clinicians should take a different approach when assessing an elderly patient who has a loss of ACL integrity. A loss of ACL integrity also places this cohort at an increased risk of falls and subsequent increased risk of morbidity and mortality. Knee buckling is a common symptom of knee instability and may be caused by muscle weakness and balance difficulties and has been shown to increase the frequency of falls and fall-related injuries [2]. Muscle strengthening exercises, improved joint proprioception and indeed even surgical intervention such as a joint replacement may stabilize the knee and as such help maintain older individuals' health and quality of life.

Furthermore, clinicians should consider performing early MRI imaging in older adults who injure their knee. MRI has repeatedly shown a higher specificity and sensitivity for the assessment of total joint morphology following injury thus allowing for improved assessment of early disease development that precedes the development of both joint space narrowing and osteophyte formation on a plain radiograph [3]. Changes such as the development of synovitis and BMLs which occur in early knee OA have been found to correlate positively with patient reported knee pain, whilst

structural radiographic correlates of OA do not correlate significantly to the overall pain experience of an individual, particularly at mild to moderate radiographic disease [3].

Future Research Directions

The optimal goal of medical research is to identify disease risk factors and pathophysiology to ultimately produce disease prevention strategies and to isolate drug targets to provide symptomatic relief for patients. Presently, therapeutic interventions for OA are palliative and consist primarily of analgesia and surgical intervention regardless of the cause of disease development. In the absence of pharmacologic agents that can modify disease we need to instead focus on the modifiable risk factors, namely obesity, alignment and injury prevention, for prevention of disease incidence, progress and relief of symptoms. This thesis identifies that injury to the ACL significantly increases an individual's risk of incident radiographic knee OA and it is hoped that finding suitable disease modifying agents will prevent incidence and progression of knee OA following injury.

Focusing on injury in the aged knee is currently a very under investigated field of research. The results of this thesis firstly need to be confirmed in longitudinal studies with a larger, ACL-focused cohort containing a larger number of ACL injured knees across a wide spectrum of participant ages with a specific focus on an elderly cohort with a documented history of knee injury. Confirmation of these results followed by further comprehensive radiographic investigations of the incidence of tissue damage will aid us to establish an exact time line of disease progression and how this differs from primary degenerative knee OA and secondary, post-traumatic knee OA in knees injured in adolescence.

Autoimmune and inflammatory disorders such as rheumatoid arthritis and spondylarthropathies have benefited greatly from the advent of biological agents that

target specific pro-inflammatory cytokines and prevent the onset and progression of erosive arthritis. It is hoped that the establishment of a timeline of OA disease progression will allow for the identification of appropriate disease modification strategies that will target tissues directly affected following traumatic injury to the ACL and thus preventing the promotion of the inflammatory cascade that occurs following injury, which undoubtedly causes further destruction to the joint.

Ultimately, it is imperative that the relationship between the age of knee injury and OA incidence is studied with a more robust cohort in the future in order to identify whether older adults who injure their knee are at a potentially increased risk of joint instability, disability and ultimately joint failure in a truncated time period. Only then would this lead to prompt recognition of this at-risk population after injury, the production of interventions to delay or prevent the onset of knee OA incident as well as techniques or training strategies to prevent initial knee injury amongst the elderly.

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APPENDIX

Osteoarthritis: What Does Imaging Tell Us about Its Etiology?

Victoria L. Johnson, Bach App Sc (Ex Sp Sc Nutr)[1] Bruno M. Giuffre, MB, BS, FRANZCR[2]
David J. Hunter, MBBS, PhD, FRACP[3,4]

[1] Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
[2] Department of Radiology, Royal North Shore Hospital, St. Leonards, Sydney, New South Wales, Australia
[3] Department of Rheumatology, Royal North Shore Hospital, St. Leonards, NSW Australia
[4] Northern Clinical School, University of Sydney, Sydney, New South Wales, Australia

Address for correspondence and reprint requests David J. Hunter, MBBS, PhD, Department of Rheumatology, Royal North Shore Hospital, Pacific Hwy., St. Leonards, NSW 2065, Australia (e-mail: David.Hunter@sydney.edu.au).

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Abstract

Osteoarthritis (OA) is the most common joint disorder and a leading cause of disability. Due to an aging population and increasing obesity, the incidence of OA is rising. The etiology of OA is multifactorial and complex; thus prevention of OA remains challenging. Risk factors can be divided into person-level factors such as age, sex, obesity, genetics, race/ethnicity, and diet, and joint-level factors including injury, malalignment, and abnormal loading of the joints. This review provides a brief overview of the person-level risk factors and a more in-depth analysis of those at the joint level. It is only through an improved understanding of risk factors for the disease that we may be able to intervene meaningfully and prevent its occurrence.

Keywords
- osteoarthritis
- etiology
- radiography

Osteoarthritis (OA) is the most common joint disorder affecting ~15% of the population, 50% of those >65 years of age and 85% of those >75 years.[1] OA most commonly affects the hip, knee, and hand joints. Given its preference for lower extremity joints, OA is the leading cause of lower extremity disability among older adults.[1] The risk for disability attributable to knee OA is as great as the risk attributable to cardiovascular disease and greater than that caused by any other medical condition in elderly adults. OA is also the most common reason for a total knee replacement or total hip replacement.[1]

Because the prevalence of OA is projected to double by the year 2020, due in part to an aging population and an increase in the prevalence of obesity, OA is likely to have a large impact on health care and public health systems in the future.[2] This review provides a brief overview of the person-level risk factors and a more in-depth analysis of those at the joint level. It is only through an improved understanding of risk factors for disease that we may be able to intervene meaningfully to prevent its occurrence.

Defining Osteoarthritis

OA can be defined pathologically, radiographically, or clinically. Due to the ease of standardization and acquisition, radiography is often used as the standard for defining the presence and severity of OA using the Kellgren and Lawrence grading system.[3] It is more clinically relevant to measure individuals with symptomatic OA because not all persons who have radiographic OA have concomitant symptoms, and not all individuals who experience joint symptoms demonstrate radiographic OA.[4]

Incidence and Prevalence of Osteoarthritis

Approximately 6.8% of adults ≥26 years of age have radiographic hand OA,[5] and 19% of adults ≥45 years have radiographic knee OA[6] according to the Framingham Osteoarthritis Study. The Johnston County Osteoarthritis Project estimated that 28% of women ≥45 years of age had hip OA.[7] The prevalence estimates of symptomatic OA are lower because

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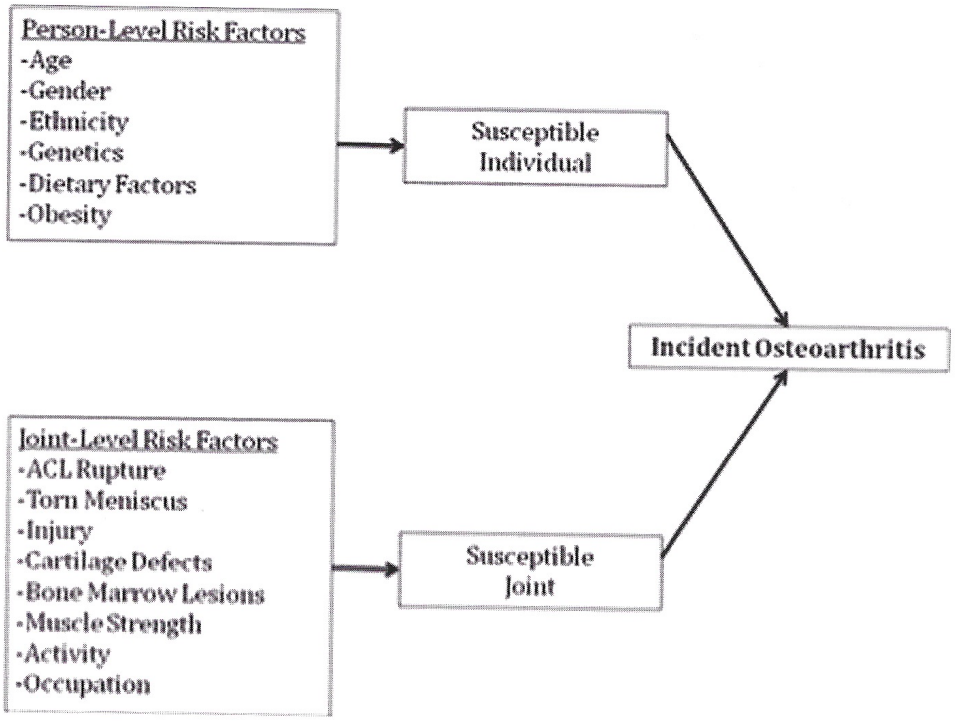

Fig. 1 Etiology of osteoarthritis. ACL, anterior cruciate ligament.

its presence is defined by a combination of radiographic OA with pain and stiffness in the joint. The Framingham Osteoarthritis Study found that the prevalence of symptomatic knee OA was 7% of adults ≥45 years of age,[6] symptomatic hand OA was approximated at 13.4% and 26.2% in men and women, respectively, in adults ≥71 years.[5] Symptomatic hip OA was present in ~10% of the Johnston County cohort.[7]

Risk Factors

OA has a multifactorial etiology so a different set of risk factors can act together to cause OA to develop in any given individual. Thus OA can be considered the phenotypic manifestation of a series of different pathways leading to a common end-stage pathology (►**Fig. 1**).

Person-Level Risk Factors

Age

Age is one of the strongest predictors of OA.[8] The exact mechanism/s behind the increased prevalence and incidence of OA with age is poorly understood but is probably a consequence of a combination of biological changes that occur with aging including cellular senescence and exposure to risk factors leading to the joint having a reduced capacity to adjust to biomechanical challenges as a consequence of age-related sarcopenia and increased bone turnover.

Gender

The prevalence and incidence of OA is higher in females than males with women more often affected with hand, foot, and knee OA than men.[9] In addition, women are more likely to experience more severe radiographic knee OA than men, particularly following menopause.[9] Gender disparities may also be caused by differences in bone strength, alignment, ligament laxity, pregnancy, and neuromuscular strength.

Racial and Ethnic Disparities

The pattern of joints affected and the prevalence of OA vary among racial groups. The National Health and Nutrition Examination Survey 1 suggested higher rates of knee OA in African American women but not men.[10] Results of the Beijing Osteoarthritis Study showed that the prevalence rate of hip and hand OA is less frequent in Asians than white populations[11] but that Chinese women had significantly higher prevalence of knee OA than white women (46.6% versus 34.8%).[12] The factors explaining these differences are poorly understood but likely relate to genetic, environmental, anatomical, and biomechanical features.

Obesity

Obesity is a very important risk factor for OA, particularly in the knee.[8] Being overweight not only antedates the development of disease but also increases the risk of radiographic progression.[8] Men and women with a body mass index (BMI) between 30 and 35 kg/m^2 have almost 4.8 and 4 times the risk of knee OA than men and women with a BMI <25 kg/m^2, respectively.[10] For every kilogram of increased body weight, the overall force across the knee in a single-leg stance increases fourfold.[12]

The Framingham Study showed that weight reduction by 5 kg provides a decreased risk for the development of knee OA by 50%,[13] confirming that obesity is a modifiable target for the prevention of knee OA. Because obesity is increasing in prevalence and is also a risk factor for OA development, it is

likely that more individuals will be affected by knee OA in the future.

The relationship between body weight and hip OA is inconsistent and weaker than knee OA.[8,14] Obesity is also associated with hand OA, confirming that obesity may also provide some metabolic and inflammatory effects.[15]

Genetics

OA in all of its forms appears to be strongly genetically determined. Genetic factors account for at least 60% of hip and hand OA, with knee OA up to 40%.[16] However, OA is a polygenic disease, so the overall effect of each individual susceptibility gene is only moderate. Genomewide association studies have identified the growth differentiation factor 5 gene (*GDF5*) and the 7p22 chromosome as the main contenders for OA susceptibility. Other signals, such as *DIO2, SMAD3,* and *ASPN,* may also be involved in OA susceptibility.

Diet

Continuous exposure to oxidant species contributes to the development of age-related diseases such as OA by damaging articular tissues.[17] High vitamin C intake was shown to reduce the progression of radiographic knee OA threefold as well as reducing the risk of developing knee pain.[17] Vitamins D and K are associated with several aspects of bone and articular cartilage metabolism. A diet deficient in vitamins D and K can increase the progression of knee and hip OA, and an adequate intake of vitamin D might slow disease progression.[18,19] Fish oil contains the polyunsaturated acid omega-3, and this fatty acid has been found to be chondroprotective and an anti-inflammatory agent in in vitro studies.[20]

Joint-Level Risk Factors

Occupation

Repetitive joint use has been associated with an increased risk of OA. Studies have found that individuals whose occupations require squatting, kneeling, or carrying heavy loads have twice the risk of developing knee OA than occupations that do not require physical activity.[21] Prolonged standing and lifting have also been associated with hip OA.[22] Occupations that require dexterity, particularly the repeated use of a pincer grip, have an increased risk of developing OA at the distal interphalangeal and the metacarpophalangeal joints.[23]

Exercise and Physical Activity

The issue of repetitive joint use may also be pertinent for physical activity. Multiple population-based studies[24,25] have found that high levels of physical activity increase the risk of developing knee and hip OA. However, when sporting injuries and joint impact are accounted for, there is no evidence to support a deleterious effect of physical activity on normal joints.[26]

Conversely, there is an association between developing OA and participating in an elite-level sport. Elite athletes who participate in repetitive high-intensity and high-impact sports (such as running, dancing, tennis, squash, and team sports) have an increased risk of developing radiographic hip and knee OA when compared with an age-matched nonelite cohort.[26] Whether this is solely due to sport participation or as a result of injury is unclear. Thus when considering an individual's risk of developing OA due to exercise, the most important aspects to consider are the type of sport, its intensity, and a history of joint injury.

Internal Joint Risk Factors

Anterior Cruciate Ligament Injury

The anterior cruciate ligament (ACL) provides the main restraint of anterior tibial translation at the knee, and as such it is the most commonly injured knee ligament, particularly in sports that require pivoting. The incidence of ACL rupture is 81 per 100,000 annually between the ages of 10 and 64 years.[27] For high-risk sports, the risk of rupturing the ACL is up to 1000 times higher than the general population.[28] The risk of rupture is higher in adolescents than adults and up to five times higher in adolescent women than men.[29,30] Thus, given that the most of the patients who experience an ACL injury are adolescents, ACL injuries may lead to a large number of individuals with early-onset knee OA[28] because individuals with a knee injury have a five times increased risk of developing knee OA.[31]

An isolated ACL injury is not common, and injury of the ACL is associated with injuries to the cartilage, subchondral bone, menisci, and other ligaments[28] as shown in ►**Fig. 2**. The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. It has been postulated that most of the tissue damage is related to the large forces required to injure the ACL.[29] In addition, intra-articular bleeding commonly occurs with the initial injury, as well as the surgical repair, causing both an acute and sustained release of inflammatory cytokines and proteases from joint tissues[30] that may lead to further damage of the type 2 collagen network.

Changes in the static and dynamic loading of the injured knee are also apparent due to the lack of a functional ACL. There are significant differences in the tibiofemoral motion of ACL-deficient knees with respect to healthy controls.[32] There is increased tibial internal rotation and posterior translation throughout the stance phase of walking, altering tibiofemoral loading patterns. This changes the region of cartilage that is in contact during weightbearing, causing increased loading of areas that were not conditioned to constant load prior to injury.

Two studies focusing on soccer players found a high prevalence of knee OA in both female[33] and male[34] athletes. Twelve years after an ACL injury, 41% and 51% of men and women exhibited radiographic knee OA, respectively. None of the people reported OA in their noninjured contralateral knee. These results are consistent with a review by Lohmander and colleagues who suggested that 50% of individuals who experience a traumatic ACL injury develop OA.[28] Yet despite these studies, a 2008 systemic review concluded that the prevalence of knee OA with an isolated ACL rupture

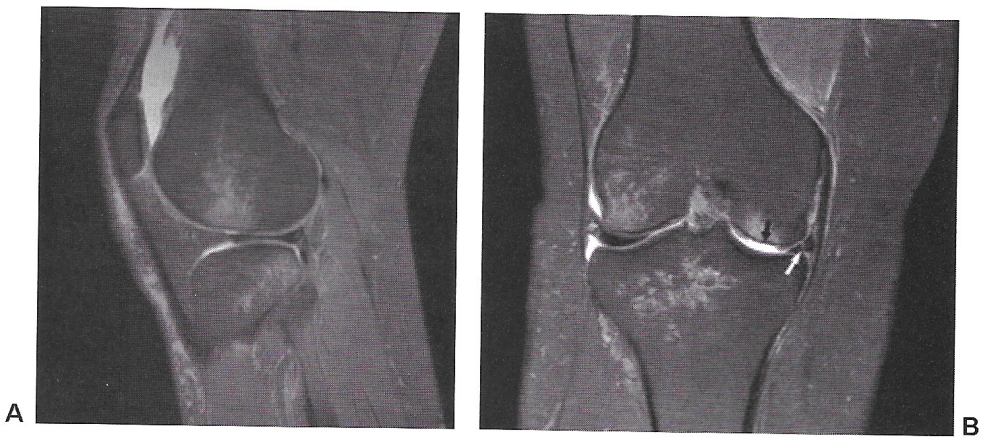

Fig. 2 A 46-year-old woman with a recent acute twisting injury to the knee resulting in an anterior cruciate ligament (ACL) tear, as well as a tear of the medial meniscus and a focal cartilage defect of the medial femoral condyle. (A) Sagittal fat-suppressed fast spin-echo proton-density image of complete tear of ACL with characteristic impaction bone bruises from the translational component of injury. (B) Coronal fat-suppressed fast spin-echo proton-density image with vertical tear of the posterior medial meniscus (white arrow) and 10-mm full-thickness cartilage loss of medial femoral condyle (black arrow).

was as low as 13%.[35] Thus, with such a large range in the prevalence of knee OA attributable to ACL injuries, the study methods and outcome measures used to ascertain OA need to be more consistent across studies.

Studies have also looked at the prevalence of knee OA in people who have undergone ACL reconstructive surgery versus those who had conservative treatment. Both these treatment groups showed the same prevalence of knee OA,[36,37] leading a Cochrane review to declare there is insufficient evidence to determine which method of treatment is best for ACL injuries.[38] A study of European handball players found that 22% of those who returned to their sport post-ACL reconstruction would later reinjure their ACL.[39] If long-term joint health is the primary concern, this raises questions as to whether returning to sports that involve pivoting is really in the athlete's long-term interest with regard to joint health. Consequently, it is important to note that although surgery may repair the ligament in the short term, it does not prevent the development of knee OA in the long term.[35,36] Nor does it protect the knee from reinjury. This highlights that the major intra-articular changes that occur at the time of injury may confer the risk to later OA development.

Paradoxically, knee OA may also cause injury to the ACL. Amin et al[40] found that among individuals with established radiographic knee OA, between 20% and 35% had an incidental ACL tear (►**Fig. 3**). Established OA may cause degenerative changes within the ACL and thus make it prone to rupture without major trauma. In addition, an ACL tear in established knee OA will accelerate the progression of knee OA.[41]

Injury to the Meniscus

The meniscus plays a protective role in each of the tibiofemoral compartments, acting as a shock absorber and aiding the distribution of load across the joint surface, thus contributing to joint stability and proprioception.

There are two main meniscal lesions; traumatic and degenerative. Traumatic lesions usually occur as a result of an acute trauma in younger, active individuals, are often

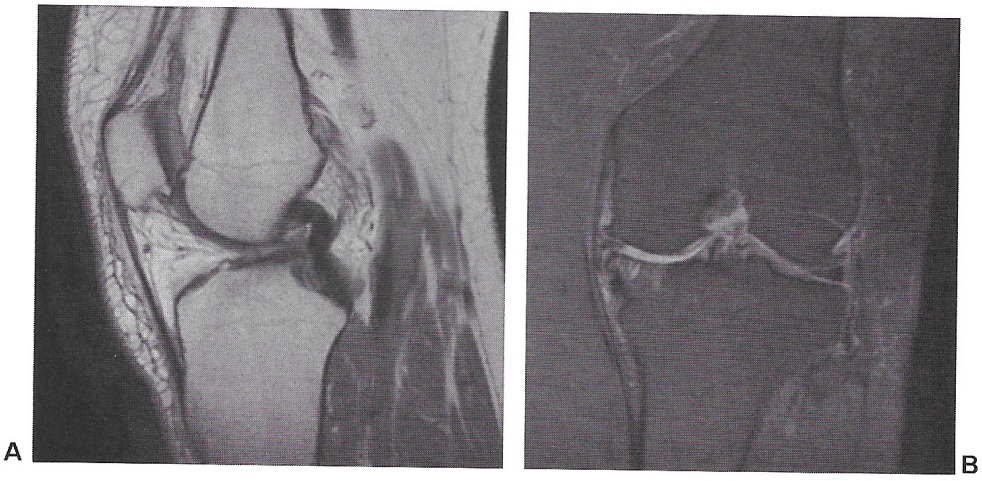

Fig. 3 A 65-year-old woman with extensive medial compartment osteoarthritis and chronic anterior cruciate ligament (ACL) tear. (A) Sagittal fast spin-echo proton-density image with redundant posterior cruciate ligament as a result of ACL deficiency. (B) Coronal fat-suppressed fast spin-echo proton-density image with marked long-standing cartilage loss and secondary tibial subchondral marrow lesion and cyst formation.

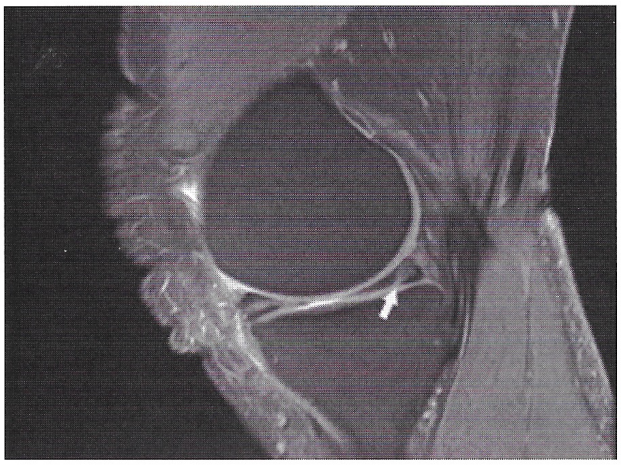

Fig. 4 A 74-year-old with degenerative horizontal tear of posterior medial meniscus and thinning of articular cartilage: Sagittal fat-suppressed fast spin-echo proton-density image demonstrating a horizontal tear of the posterior medial meniscus (white arrow).

symptomatic, and have been shown to carry an increased risk of developing knee OA.[42] Degenerative lesions, as shown in ►**Fig. 4**, often occur in middle-age and elderly individuals with knees that have already been compromised by OA.[42]

An analysis of meniscal lesions found that a greater number of tears occur in the medial than the lateral meniscus (37% versus 16%).[43] Because the medial meniscus is firmly attached to the joint capsule, it is more likely to become trapped between the femoral condyle and the tibial plateau under extreme forces. The lateral meniscus is more mobile; therefore it is injured less frequently.

The Framingham Study found that 82% of people who displayed radiographic knee OA had meniscal damage. Most of them had degenerative lesions.[44] Bhattacharyya et al found that 91% of individuals who had symptomatic knee OA had a meniscal tear.[45] Intrameniscal signal changes were a frequent finding even when a tear was not present on MRI. These signals may signify the beginnings of meniscal deterioration and thus represent a precursor to a degenerative lesion.[46] The long-term radiographic outcome for those people with a degenerative lesion was found to be worse than those with traumatic lesions[42] including an increased risk for early-onset OA.[28]

Recent literature has argued as to whether or not damage to the meniscus is a cause or a consequence of knee OA.[47] Morphologically, normal menisci are rarely found in patients with knee OA, suggesting there is a significant disorder of the meniscus involved with the development of OA.[44,45] Middle-age and elderly individuals who have radiographic meniscal damage are at a higher risk of developing knee OA, as evidenced in ►**Fig. 5**, even without cartilage loss, than in those who have normal menisci.[48] This suggests that damage to the meniscus antedates radiographic cartilage changes. An example of this is the defunctioning of the medical meniscus with a tear at the posterior root with consequent accelerated degeneration.[49]

Cartilage destruction due to the pathologic processes that are active during the early stages of OA could also affect meniscus and ligament integrity. Thus knee OA may also cause meniscal lesions and act to further accelerate the disease.[50]

Surgery is the most common form of treatment for injuries to the menisci. However, just like ACL reconstructions, surgery might be able to fix the meniscus in the short term, but it cannot prevent the incidence of symptomatic radiographic knee OA, regardless of whether a total or partial meniscectomy is performed.[42,48] Meniscal replacement surgeries including the use of allogeneic, xenogeneic, and artificial menisci have been tried in younger patients, but the transplant survival is variable and long-term results are lacking.[28]

Cartilage

Articular cartilage is both aneural and avascular; thus cartilage is unable to produce pain, stiffness, inflammation, or any other symptom of OA.[51] OA was once considered a primary disorder of the articular cartilage, but now it is widely

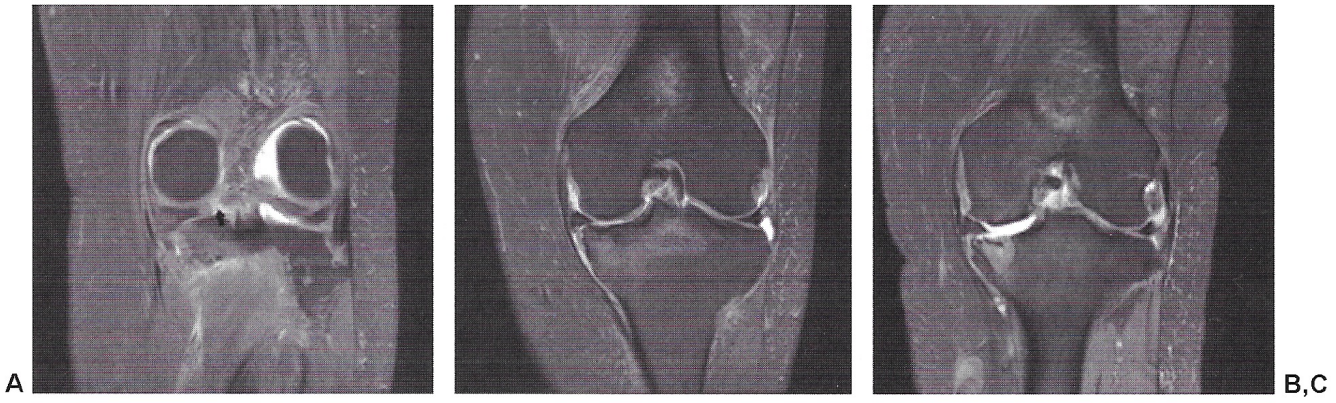

Fig. 5 A 70-year-old woman who had a minor injury, with a defunctioning medial meniscal root tear and displacement of the body of meniscus. (A) Coronal fat-suppressed fast spin-echo proton-density image with tear of the medial meniscal root. (B) Coronal fat-suppressed fast spin-echo proton-density image with medially displaced and dysfunctioned medial meniscus. (C) A follow-up study 10 months later demonstrated rapid loss of articular cartilage and a focal subchondral collapse of the tibial plateau. Coronal fat-suppressed fast spin-echo proton-density image with virtual loss of all articular cartilage over femoral and tibial surfaces as well as minor subchondral collapse, attrition, and bone marrow lesion in the proximal medial tibia.

appreciated that multiple structures are involved and affected in the development of OA.

Cartilage pathology in OA is a balance between synthesis and degradation of the articular cartilage matrix. Excessive matrix degradation increasingly overwhelms matrix synthesis due to an excess of inflammatory catabolic signals, matrix metalloproteinases (MMPs), and aggrecanases that act to further degrade the cartilage matrix.[51,52]

Adult chondrocytes rarely divide; thus they can accumulate reactive oxidative species that can cause altered cell viability and chondrocyte death. Recent evidence suggests that during the development of OA, there is increased cell proliferation and an upregulation of synthetic activity resulting in clusters of chondrocytes.[51,52] Despite this, these cells are not able to maintain the integrity of the cartilage matrix, mainly due to their inability to respond to growth factors, and thus further contribute to the increased matrix degradation and the destruction of type II collagen.[51,52] These changes are also accompanied by cartilage surface fibrillation and the production of fibrocartilage.[52]

It was previously suggested that cartilage thinning poses an increased risk for OA and may in fact represent the initial pathology of OA.[53] However, more recent studies suggest that early osteoarthritic cartilage may be thicker and swollen with water due to the disruption of the collagen network along with altered proteoglycans. It was proposed that focal areas of denuded cartilage and increased cartilage thickness may be part of the initial evolution of the disease and that cartilage defects may occur in early knee OA and precede cartilage volume loss.[54,55] In patients with symptomatic OA, progression of cartilage defects over 30 months was found in 46% and 22% for the medial and lateral tibiofemoral compartments, respectively. Furthermore, cartilage defects are also associated with bone expansion, bone marrow lesions (BMLs), meniscal injuries, and ACL rupture, suggesting that they have multiple causes.[55] MRI is able to capture these initial structural (and occasionally ultrastructural) changes in the earliest phases of the disease; changes such as joint space narrowing as detected by radiographs emerge at a much later stage.[55]

Subchondral Bone

Bone cells are more able to self-repair and modify their surrounding extracellular matrix than articular cartilage.[51,52] Subchondral bone undergoes adaptations during the development of OA including an increase in subchondral plate thickness, sclerosis, joint space narrowing, reduced matrix mineralization, increased cancellous bone volume, formation of osteophytes at the joint margins, development of bone cysts, and advancement of the tidemark associated with vascular invasion of the calcified cartilage. These changes may cause alterations in the adjacent joint surfaces, which in turn will change the joint congruity and hence progress the disease.[52,56]

It is the adaptive capacity of bone that underlies the more rapid appearance of detectable skeletal changes, especially after joint injuries or with altered mechanics. The presence of BMLs correlates with the severity of pain as well as the areas of greatest cartilage loss[52,56] (►**Fig. 6**). BMLs were present in 77.5% of patients who experienced painful knees compared with only 30% of those who reported no knee pain.[56] Furthermore, BML have been found to be compartment specific for cartilage progression. In terms of bone abnormalities, BML is the only effective risk factor for predicting knee OA progression.[56]

Recent studies[57,58] in asymptomatic populations discovered that the development of new BMLs in knees that contained no BMLs at baseline were associated with the progression of tibiofemoral cartilage defects and loss of cartilage volume reflecting early cartilage pathology. This suggests that not only can BMLs propagate OA progression, but they may also play an important role in the pathogenesis of knee OA.

Synovitis and Effusion

Synovitis and effusion are frequently present in OA and are directly responsible for several clinical symptoms and reflect the structural progression of the disease[53] (►**Fig. 7**). Synovial inflammation is focused in areas adjacent to damaged cartilage and bone and can cause the release of proteinases,

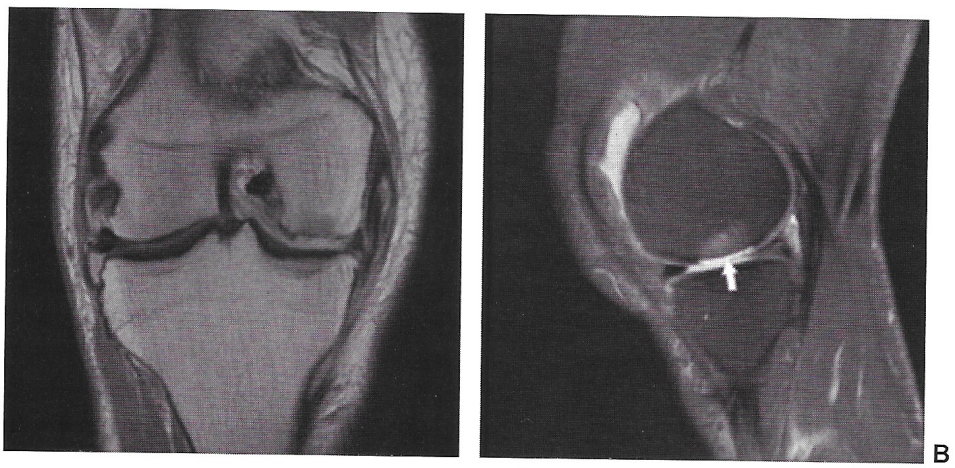

Fig. 6 A 70-year-old man with an injury to the knee resulting in focal cartilage loss. (A) Coronal fast spin-echo proton-density image with focal defect. (B) Sagittal fat-suppressed fast spin-echo proton-density image demonstrating focal cartilage defect (white arrow) with underlying bone marrow lesion and degenerative changes in the posterior medial meniscus.

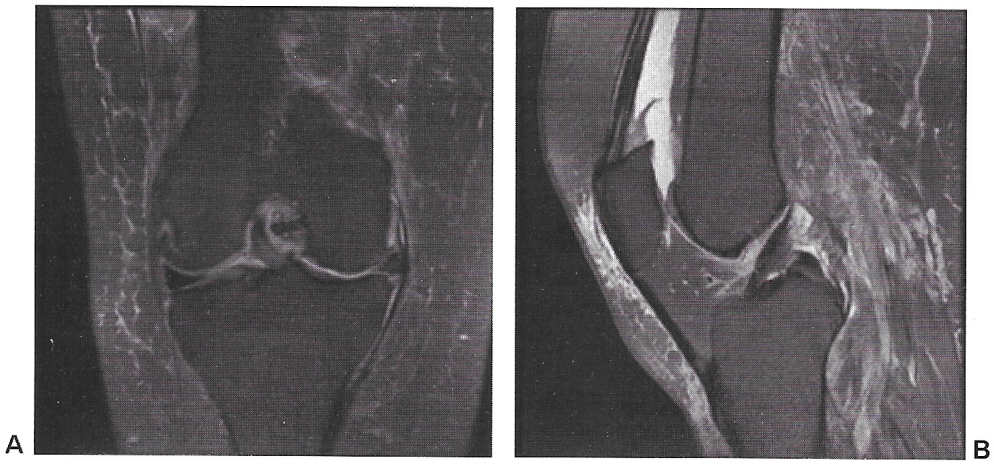

Fig. 7 A 65-year-old man with long-standing known osteoarthritis of the knee and an episode of synovitis/effusion. (A) Coronal fat-suppressed fast spin-echo proton-density image with moderate cartilage loss in the medial compartment as well as degeneration of the medial meniscus. (B) Sagittal fat-suppressed fast spin-echo proton-density image with prominent cartilage loss of the patellofemoral joint and a large suprapatellar effusion.

inflammatory cytokines, MMPs, and aggrecanase[53] that further accelerates the degradation of cartilage. The release of these inflammatory mediators, as well as the formation of osteophytes, may act to irritate sensory nerve endings within the synovium causing pain. An MRI analysis of people with knee OA showed that synovial thickening was greater among those who experienced knee pain than in asymptomatic people.[59]

The clinical symptoms of inflammation along with the presence of histologic inflammation in synovial tissue and cartilage lesions at the border of inflamed synovium are strong indicators that synovitis plays a pivotal role in the development of OA. Synovial inflammation also perpetuates disease progression. Roemer et al[60] reported that individuals who displayed moderate to severe baseline synovitis had an increased risk of rapid cartilage loss.

Mechanical Factors

Quadriceps Strength

Quadriceps femoris is the primary antigravity muscle of the lower limb and serves to decelerate the lower limb during ambulation as well as to stabilize the knee.

Quadriceps weakness is common among OA patients. Baseline knee extensor strength was reduced in women with no knee radiographic changes at the initial examination but who developed knee OA 30 months later.[61] This was confirmed by Baker et al,[62] who found that patients with asymptomatic patellofemoral and tibiofemoral radiographic knee OA had reduced quadriceps strength when compared with those who did not have OA.

Additionally, quadriceps weakness may also increase the risk of structural damage. For every 5-kg increase in extensor strength, Slemenda et al found an associated 20% and 29% reduction in the odds of developing radiographic knee OA and symptomatic knee OA, respectively.[61]

Alignment

A shift from neutral will alter load distribution across the knee. Thus malalignment may contribute to abnormal mechanical forces. Knee malalignment is one of the strongest predictors of knee OA progression. A prospective cohort study showed that abnormal alignment was strongly associated with increased structural degradation in the compartment that was under greatest compressive stress.[64] Medial progression of knee OA was four times more likely in individuals with varus alignment; lateral progression was five times more likely in individuals with valgus alignment.[63] BML as well as rapid cartilage loss displayed on MRI are also associated with knee malalignment.[64] It is important to note that no study as yet has documented the slowing of disease progression when alignment is corrected.

The association between incident knee OA and malalignment is less apparent. The Rotterdam Study found that individuals with varus and valgus knee alignment had an odds ratio of 2.06 and 1.54 of developing radiographic knee OA, respectively.[65] However, these results were not supported by the Framingham Study.[66]

Summary

As the prevalence of OA in the population continues to rise, so does the substantial burden placed on the health care system. The etiology of OA is multifactorial and complex, and thus prevention of OA remains challenging. Risk factors for developing OA are different for each joint. The use of advanced imaging, the measurement of systemic and local biomarkers, combined with the improved methods of measuring symptoms, will ultimately help lead to the development of disease-modifying pharmaceuticals and improved nonpharmacologic treatments of OA.

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The epidemiology of osteoarthritis

Victoria L. Johnson, Bach. App. Sc (Ex. Sp. Sc. Nutr) Honours, Medical Student [a,1], David J. Hunter, Professor [b,*]

[a] Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[b] Rheumatology Department, Royal North Shore Hospital and Kolling Institute, University of Sydney, Sydney, NSW, Australia

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A B S T R A C T

Osteoarthritis (OA) is a leading cause of disability and its incidence is rising due to increasing obesity and an ageing population. Risk factors can be divided into person-level factors, such as age, sex, obesity, genetics, race/ethnicity and diet, and joint-level factors including injury, malalignment and abnormal loading of the joints. The interaction of these risk factors is complex and provides a challenge to the managing physician. The purpose of this review is to illustrate how each of these factors interact together to instigate incident OA as well as to outline the need for ongoing epidemiologic studies for the future prevention of both incident and progressive OA. It is only by understanding the impact of this disease and the modifiable risk factors that we will be able to truly target public health prevention interventions appropriately.

Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting approximately 15% of the population [1]. Due to its predilection for lower extremity joints such as the knee and hip, OA is the leading cause of lower extremity disability amongst older adults with an estimated lifetime risk for knee OA being approximately 40% in men and 47% in women. The risks are higher still among individuals who are classified as obese [2]. Currently, OA is one of the most commonly diagnosed diseases in general practice, with its prevalence projected to double by the year 2020 due largely to an ageing

* Corresponding author. Tel.: +61 2 9926 7087; fax: +61 2 9906 1859.
E-mail addresses: vjoh6545@uni.sydney.edu.au (V.L. Johnson), David.Hunter@sydney.edu.au (D.J. Hunter).
[1] Tel.: +61 2 9543 4378.

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population and an ever-increasing prevalence of obesity [2]. This has been demonstrated in recent estimates from US data which indicate that the prevalence of clinical hand, hip or knee joint OA has increased from 21 million US adults aged 25 years or older in 1995 to 27 million adults in just over a decade [2].

A number of reviews [3,4] have been conducted on this theme recently; however, this narrative review differs in that its purpose is not only to examine the multitude of risk factors associated with OA but also to highlight the areas of aetiology that require more rigorous investigation and to address issues related to interventions and future therapies for patients suffering with OA.

Prevalence and incidence of OA

The Framingham Osteoarthritis Study found that 6.8% and 19% of adults exhibited radiographic hand [5] and knee OA [6], respectively. Similarly, both hip and knee OA had a prevalence of 28% of African–American and Caucasian men and women in the Johnston County Osteoarthritis Project. This potentially may have been related to genetic, anatomic or occupational differences [7,8].

Symptomatic OA prevalence estimates are lower as its presence is defined by a combination of symptoms such as pain, aching and stiffness as well as radiographic features. Framingham reported the prevalence of symptomatic hand OA to be 26% and 13% in women and men, respectively, and knee OA to be 7% [5]. The Johnston County cohort reported prevalence rates of 17% for symptomatic knee OA [7,8] and 10% for symptomatic hip OA [7]. However, not all individuals with radiographic OA have concomitant symptoms. Furthermore, risk factors for structural disease and symptomatic disease may not be the same.

Defining OA

OA can be defined pathologically, radiographically or clinically. Due to the ease of standardisation and acquisition, radiography is often used as the standard for defining the presence and severity of OA using the Kellgren and Lawrence (KL) [9] grading system [10]. This system scales OA severity on a scale of 0–4 with >2 defining radiographic OA. The KL grading system has been used for hand and hip OA, but for the knee it can only be used to define tibiofemoral OA with the distinct radiographic feature of X-rays defining OA of the patellofemoral joint. Currently, there is no standard magnetic resonance imaging (MRI) definition of OA although a preliminary definition including cartilage lesions, osteophytes, bone marrow lesions (BMLs), synovitis and effusion has been described [11].

Risk factors for OA

OA appears to be the result of a complex interplay between mechanical, cellular and biochemical factors leading to common end-stage pathology, as such a different set of risk factors acting together may cause OA onset in any given individual (see Fig. 1). This review focusses on the influence of these risk factors on the aetiology of OA and its symptomatic presentation as well as outlines the need for ongoing epidemiologic studies for the future prevention of both incident and progressive OA. It is only by understanding the impact of this disease and the modifiable risk factors that we will be able to truly target public health prevention interventions appropriately.

Person-level risk factors

Age and gender

Age is one of the strongest predictors of OA [12]; however, the exact mechanism/s behind the increased prevalence and incidence of OA with age is poorly understood. A combination of changes including the capacity for joint tissues to adapt to biomechanical insults, biological changes such as cellular senescence as well as having a reduced capacity to adjust to biomechanical challenges as a consequence of age-related sarcopenia and increased bone turnover are likely contributing factors.

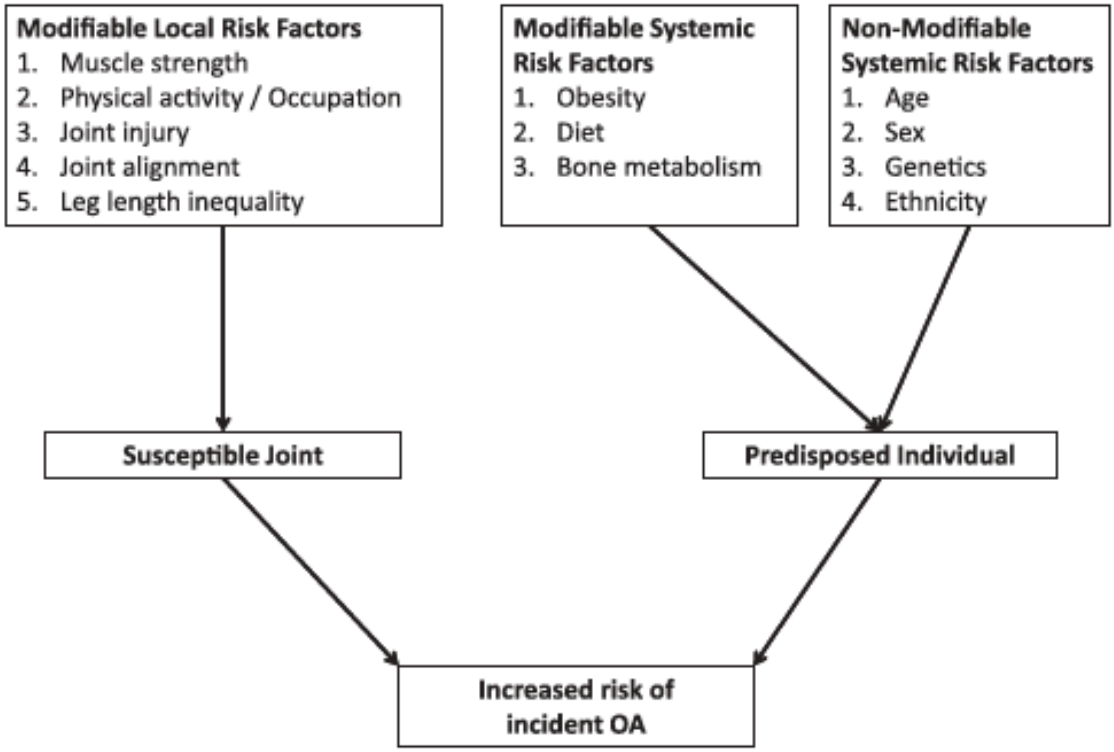

Fig. 1. Potential risk factors for susceptibility to OA incidence, each with differing degrees to support their association.

Females are associated with a higher prevalence and severity of OA and are more often affected with hand, foot and knee OA than men [13]. In addition, women are more likely to suffer more severe radiographic knee OA then men, particularly following menopause [13]. The increase in incidence of OA at the time of menopause has led to hypotheses regarding the role of oestrogen in OA. Oestrogen may unmask the symptoms of OA by enhancing pain sensitivity; however, results from observational studies and clinical trials have been conflicting [14,15]. Gender disparities may also be caused by differences in bone strength, alignment, ligament laxity, pregnancy and neuromuscular strength. Women may also have a reduced volume of knee cartilage than men, but it is not clear if this could contribute to accelerated cartilage loss.

Genetics

OA in all of its forms appears to be strongly genetically determined with genetic factors accounting for at least 60% of hip and hand OA and up to 40% of knee OA [16]. Whilst many studies focus on OA prevalence, many genes have been identified in playing a role in OA pathophysiologic pathways and thus may contribute to OA risk. Genes for vitamin D receptors, insulin-like growth factor 1 [12], type 2 collagen [17] and growth differentiation factor 5 (GDF5) [18] may provide targets for future pharmaceutical approaches. Linkages have been made between an area of 'chromosome 2q' and nodal OA [19], hip OA in women and chromosome 11q [20], 'chromosome 7q22' and knee OA [21] and GDF5 (a bone morphogenetic protein expressed in articular and skeletal structures) and knee and hip OA in meta-analytic studies [22,23]. Other signals such as DIO2, SMAD3 and ASPN may also be involved in OA susceptibility. Many of these findings are yet to be confirmed in all ethnicities and populations possibly due to inadequate phenotypic assessment of controls and social stratifications.

Obesity

Obesity has become a global problem leading to excess morbidity and mortality. There is considerable evidence indicating that obesity represents one of the most important risk factors for OA at peripheral joints such as the knee and hip [24]. As obesity is increasing in prevalence and is also a risk factor for OA development, it is thus likely that more individuals will be affected by knee OA in the future.

Being overweight not only antedates the development of disease but also increases the risk of radiographic progression [12]. A recent meta-analysis [24] found that a dose–response relationship exists between obesity and the risk of knee OA. For every 5-unit increase in body mass index (BMI), there is an associated 35% increased risk of knee OA. The magnitude of the association was significantly stronger in women than that found in men. Furthermore, Lohmander et al. [25] found a relative risk of knee OA to be 8.1 for patients with a BMI > 30 in a Swedish population.

Conversely, the Framingham Study showed that weight reduction by 5 kg provides a decreased risk for the development of knee OA by 50% [26], the findings also supported by a more recent meta-analysis [27]. In a separate study, the population attributable risk for knee OA due to obesity was 29% and was higher in populations in which the prevalence of obesity was even higher [28].

The relationship between body weight and hip OA, however, is inconsistent and weaker than that for knee OA [12,29]. Obesity is also associated with hand OA conferring the possibility that obesity may also provide some metabolic and inflammatory systemic effects. Greater weight has been associated with both incident radiographic and incident symptomatic hand OA [30].

Diet

Reactive oxygen species can accumulate with age and can be generated in joints, damaging articular tissues [31]. Furthermore, animal studies have emphasised the importance of early life nutrition as a contributor to OA susceptibility but these effects have yet to be established in humans [32].

As vitamin D is associated with several aspects of articular cartilage and bone metabolism, it has been postulated that low levels of vitamin D may increase the incidence and progression of knee and hip OA [31,33,34]. However, the relationship between vitamin D and OA has been conflicting. Previous studies have found that subjects with low to moderate levels of vitamin D (3–347 IU/d) were at an increased risk of incident hip OA and further progression of knee OA [31,33,34]. In addition, low serum levels of vitamin D also predicted loss of joint space and increased osteophyte growth in knee OA [35]. Despite this, recent randomised controlled trials concluded that there was no demonstrable cartilage loss on MRI in subjects with low levels of vitamin D [35,36].

Antioxidant vitamins may also play a role in OA. Low intake of vitamin C has been associated with an increased risk of knee OA progression [31] and, similarly, high vitamin C intake has been shown to reduce the progression of radiographic knee OA threefold as well as reducing the risk of developing knee pain [35].

Vitamin K is an important regulator of bone and cartilage mineralisation. Low levels of plasma phylloquinone (<0.5 nmoles/l) have been shown to increase the prevalence ratios for OA, osteophytes and joint space narrowing in the hand and osteophytes in the knee [37]. Kashin–Beck osteoarthropathy has been associated with iodine and selenium deficiency [38,39].

Conversely, no evidence has been found that a high intake of any of the aforementioned antioxidant nutrients reduces the incidence of knee OA [31] or affects the volume of cartilage. Further studies are required to better refine the association between OA and dietary factors.

Joint-level risk factors

Occupation and physical activity

Repetitive joint use has been associated with an increased risk of OA. Studies have found that individuals whose occupations require squatting or kneeling have twice the risk of developing knee OA than occupations that do not require physical activity, particularly among those who are overweight or whose jobs required carrying or lifting [40]. Hip OA has also been associated with prolonged standing and lifting [41]. Occupations that require increased manual dexterity have been associated with features of hand OA [42].

The issue of repetitive joint use may also be relevant for physical activity. Physical activity may potentially be detrimental if it places undue load on the joint despite the observed benefits of strengthening periarticular muscles to help stabilise the joint. A recent review by Hansen et al. [43] failed to find evidence to support an association or causal relationship between low- and moderate-

distance running and hip and knee OA in general population studies defined as incident radiographic or symptomatic OA. The review also produced inconclusive evidence regarding high-volume running and OA development [43] suggesting that, in the absence of joint injury, the risk of OA development due to running and exercise is minimal. Limited information exists regarding the effect of running and the development of OA at the ankle and the lumbar spine.

Conversely, there does appear to be an association between elite-level athletes and OA development due to the highly repetitive, intense and high-impact nature associated with sports such as tennis, squash and team sports. This cohort confers an increased risk of developing radiographic hip and knee OA when compared to an age-matched, non-elite cohort [44]. It is unclear, however, whether this association is solely due to sports participation or as a result of injury. In two studies of athletes, the increased risk of OA appeared to be related to knee injury amongst soccer players rather than due to training loads [45,46].

Post-traumatic knee injuries

Multiple intrinsic factors affect a joint's ability to withstand destructive forces including the thickness of the articular cartilage, the strength of the bone adjacent to the joint, ligament and muscle strength and neuromuscular control of the joint. Yet, despite these factors and the introduction of biomechanical training programmes initiated into schools and elite sporting organisations, the knee remains one of the most commonly injured joints. In the context of OA, the most important injuries are those resulting in the rupture of the anterior cruciate ligament (ACL), which is often accompanied by damage to the articular cartilage, subchondral bone and collateral ligaments and, importantly, damage to the menisci is observed in approximately 65–75% of ACL-injured knees [47]. The risk of ACL rupture is higher in adolescents and up to 70% higher in high-risk sports than in the general population [48].

ACL rupture, traumatic meniscal tears and direct articular cartilage damage sustained during injury are strongly linked to the subsequent development of OA, with a substantial percentage of patients showing OA changes and functional disability as early as 10 years after the initial injury [47,48]. Furthermore, direct damage to the articular cartilage and the development of BMLs have been associated with matrix disruption, chondrocyte necrosis and proteoglycan loss which may not be reversible [49]. Thus, individuals who suffer a knee injury are at an increased risk of early-onset knee OA.

The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. It has been postulated that the majority of the tissue damage is related to the large forces required to injure the ACL [50]. Occult osteochondral lesions occur in 80–90% of patients with an acute ACL injury as seen on MRI suggesting that articular cartilage sustains a considerable mechanical impact at the time of injury. Most commonly, these lesions occur on the posterolateral tibial plateau and the anterolateral femoral condyle [51]. In addition, intra-articular bleeding commonly occurs with the initial injury, as well as the surgical repair, causing both an acute and sustained release of inflammatory cytokines and proteases from joint tissues [52], which may lead to further damage of the type 2 collagen network. A more recent study demonstrated that the lack of a functional ACL changes the static and dynamic loading of the injured knee resulting in a change to the region of cartilage that is in contact during weight bearing. This may cause increased loading of areas that were not conditioned to constant load prior to injury [53].

It is difficult to attain precise figures on the prevalence of knee OA after ACL injuries, with estimates ranging between 10% and 90% at 10–15 years after injury as studies attempting to assess the relationship between ACL rupture and OA have made use of heterogeneous populations and inconsistent radiologic classification methods. Thus, Oiestad et al. [54] suggested that post-traumatic knee OA resulting from an isolated ACL injury may be greatly overestimated with the highest-rated studies reporting a prevalence of 13% after isolated ACL rupture as compared to the 50–70% prevalence often quoted in the literature. However, when combined with damage to the meniscus, they found a higher prevalence of OA, between 21% and 40%.

Treatment of post-traumatic knee injuries

Surgery is the most common form of treatment for injuries to the ACL and the menisci. ACL reconstructions are commonly advocated on the basis that they protect against secondary injuries to the

meniscus and ligaments and therefore reduce the risk of OA development. Studies investigating the two treatment arms of surgical and conservative management for ACL rupture or meniscal tears have concluded that both treatment groups confer the same prevalence of radiographic knee OA 10–15 years after injury with the only difference being that the rate of secondary meniscal surgery was higher after nonsurgical treatment for ACL-injured knees [55–58]. A systematic review also produced similar findings [48].

Hoffelner et al. [59] found that athletes who had an isolated ACL injury and underwent surgical reconstruction conferred no increased risk of OA development in that knee when compared to the contralateral knee. This suggests that ACL reconstruction for an isolated ACL injury may prevent secondary meniscal and chondral injuries, which advance OA. Furthermore, a study of European handball players found that 22% of those who returned to their sport post ACL reconstruction would later re-injure their ACL [60]. This has led a Cochrane review to declare that there is insufficient evidence to determine which method of treatment is best for ACL injuries, as it is unclear whether ACL reconstruction decreases the incidence of OA development over the long term. Similarly, it is unclear whether ACL reconstruction or arthroscopy for treatment of meniscal tears decreases the incidence of OA [48,61,62]. Meniscal replacement surgeries including the use of allogeneic, xenogeneic and artificial menisci have been tried in younger patients but the transplant survival is variable and long-term results are lacking [48].

Thus, whilst surgery may repair an injured knee in the short term, it may not prevent the development of knee OA in the long term nor will it protect the knee from re-injury or restore normal knee kinematics. If long-term joint health is the primary concern, this raises questions as to whether returning to sports that involve pivoting is really in the athlete's long-term interest with regard to joint health. Neuman et al. [57] reported low rates of OA in patients who injure their ACL and agree to moderate their level of activity to avoid re-injury.

Local pathologic changes

OA was once considered a degenerative, primary disorder of the articular cartilage but now it is widely appreciated that multiple structures are involved and affected in the development of OA. Early osteoarthritic cartilage may be thicker and swollen with water due to disruption of the collagen network. Evidence also suggests that there is increased cell proliferation and an up-regulation of synthetic activity resulting in clusters of chondrocytes [63]. Despite this, these cells are not able to maintain the integrity of the cartilage matrix, mainly due to their inability to respond to growth factors, and thus further contribute to the increased matrix degradation and the destruction of type II collagen [63].

Damage to articular cartilage and bone may lead to adjacent synovial inflammation causing further release of proteinases, inflammatory cytokines, matrix metalloproteinases (MMPs) and aggrecanase, which acts to accelerate cartilage degradation [64]. The release of these inflammatory mediators, as well as the formation of osteophytes may act to irritate sensory nerve endings within the synovium causing pain. MRI analysis of subjects with knee OA showed that synovial thickening was greater amongst subjects who experienced knee pain than in asymptomatic subjects [65].

In patients with symptomatic OA, progression of cartilage defects over 30 months was found in 46% and 22% for the medial and lateral tibiofemoral compartments, respectively. MRI is able to capture these initial structural changes in the earliest phases of the disease, whilst changes such as joint space narrowing as detected by radiographs emerge at a much later stage [66]. Furthermore, cartilage defects are also associated with bone expansion, BMLs, meniscal injuries and ACL rupture, suggesting that they have multiple causes [66].

Normally organised menisci are rarely found in patients with knee OA, suggesting that there is a strong disorder of the meniscus involved with the development of OA [67]. Degenerative meniscal lesions often occur in middle-aged and elderly individuals with knees that have already been compromised by OA [61]. The Framingham Study found that 82% of subjects who displayed radiographic knee OA had meniscal damage with the majority suffering from degenerative lesions [67]. Bhattacharyya et al. found that 91% of subjects who had symptomatic knee OA had a meniscal

tear [68]. The long-term radiographic outcome for those subjects with a degenerative lesion has been found to be worse than those with traumatic lesions [61] including an increased risk for early-onset OA when compared to subjects who had normal menisci [48,62]. This suggests that damage to the meniscus antedates radiographic cartilage changes. Cartilage destruction due to the pathological processes that are active during the early stages of OA could also affect meniscus and ligament integrity as well. Thus, knee OA may also cause meniscal lesions and act to further accelerate the disease [69].

Bone cells are more able to self-repair and modify their surrounding extracellular matrix than articular cartilage [63,70]. Subchondral bone undergoes adaptations during the development of OA including an increase in subchondral plate thickness, sclerosis, joint space narrowing, reduced matrix mineralisation, increased cancellous bone volume, formation of osteophytes at the joint margins, development of bone cysts and advancement of the tidemark associated with vascular invasion of the calcified cartilage. These changes may cause alterations in the adjacent joint surfaces, which in turn will change the joint congruity and hence progress the disease [70,71].

It is the adaptive capacity of bone that underlies the more rapid appearance of detectable skeletal changes, especially after joint injuries or with altered mechanics. The presence of BML correlates with the severity of pain as well as the areas of the greatest cartilage loss [70,71]. BMLs were present in 77.5% of subjects who experienced painful knees compared with only 30% of subjects who reported no knee pain [71]. Furthermore, BMLs have been found to be compartment specific for cartilage progression. Subjects who were varus in alignment developed medial lesions whilst those who were valgus developed lateral lesions. In terms of bone abnormalities, BML is the only effective risk factor for predicting knee OA progression [71].

Muscle strength

Quadriceps femoris is the primary antigravity muscle of the lower limb and serves to decelerate the lower limb during ambulation, absorb limb loading as well as to provide dynamic joint stability. Thus, it has been postulated that quadriceps femoris weakness could play an important role in the genesis of knee OA.

Deficits in muscle strength, activation and proprioception are common in patients with knee OA and can occur as a consequence of OA related to disuse due to pain avoidance. Furthermore, a recent literature review concluded that there is some evidence that muscle weakness may predispose to the onset and potentially the progression of knee OA [9].

Ikeda and colleagues [72] found that the quadriceps cross-sectional area was significantly reduced in women with incident asymptomatic radiological OA, compared with women matched for age and body mass. Signs of muscle fibre atrophy have been reported in later disease states [73] with one study finding the quadriceps lean muscle cross-sectional area to be 12% lower in the affected limb compared with the contralateral limb in patients prior to knee replacement [74]. Thus, it seems likely that loss of strength associated with OA may be associated with the loss of muscle cross-sectional area.

Additionally, quadriceps weakness may also increase the risk of structural damage. For every 5-kg increase in extensor strength, Slemenda et al. [75] found an associated 20% and 29% reduction in the odds of developing radiographic knee OA and symptomatic knee OA, respectively [75]. Improvement in muscle function, especially strength, through exercise has been associated with reduced pain and improved function in people with knee OA [9].

Alignment

A shift from neutral alignment will alter load distribution across the knee; thus, malalignment may contribute to abnormal mechanical forces. Knee malalignment is one of the strongest predictors of knee OA progression with a prospective cohort study showing that abnormal alignment was strongly associated with increased structural degradation in the compartment that was under the greatest compressive stress [76]. Medial progression of knee OA was four times more likely in individuals with varus alignment, whilst lateral progression was five times more likely in individuals with valgus alignment [77]. BML as well as rapid cartilage loss displayed on MRI have also been associated with

knee malalignment [78]. It is important to note that no study as yet has documented the slowing of disease progression when the alignment is corrected.

The association between incident knee OA and malalignment is less apparent. The Rotterdam Study produced an odds ratio of 2.06 and 1.54 of developing radiographic knee OA in individuals with varus and valgus knee alignments, respectively [79]. These results were not supported by the Framingham Study, which found no association between knee joint alignment and an increased risk of incident radiographic knee OA [80].

Implications for disease prevention

Presently, therapeutic interventions for OA are palliative and are primarily analgesia and surgical intervention. In the absence of pharmacologic agents that can modify disease, we need to instead focus on the modifiable risk factors mentioned in this review, namely obesity, alignment and injury prevention, for pain incidence and disease progression.

The majority of people with OA are overweight or obese, and there is good evidence for the efficacy of weight management for OA [81]. For each kilogram of weight lost, the knee will experience a fourfold reduction in load during daily activities [82]. In practice, however, weight management is not frequently implemented [83]. If someone is overweight or obese, they should be engaged in a combination diet and exercise programme aimed at a weight reduction of >5% of body weight [81]. Exercise is often the forgotten aspect of a conservative treatment programme. Not only can exercise increase muscle strength and aerobic capacity but it also helps to facilitate weight loss. For this reason, all patients should be encouraged to participate in low-impact aerobic exercise programmes such as walking, bike riding or swimming.

It has also been suggested that targeting the pathomechanics of OA, such as correcting knee joint alignment, is effective in preventing OA progression [84]. Knee braces, orthotics, patella taping and knee osteotomies are some of the therapeutic options available to help modify joint forces [85] in an attempt to reduce both symptoms and structural changes.

Preventing knee injuries, particularly to the ACL, meniscus and chondral bone surfaces, would, in turn, help prevent a large proportion of young adults who injured their knee playing sports from developing early-onset OA. The efficacy of knee bracing to prevent knee injury has been studied, most recently in American football players, with many studies reporting relative risk reductions in injury incidence of 10–50% [86]. However, compliance is a major issue with many athletes fearing impaired athletic performance and discomfort. There is strong evidence for the role of intrinsic risk factors in the aetiology of knee injury. Studies investigating the implementation of neuromuscular and proprioceptive training programmes in young athletes have shown that these programmes may reduce ACL injuries [87,88]. These programmes are designed to train athletes to land and decelerate in a more controlled fashion with reduced valgus collapse, increased knee flexion and improved trunk control, balance and proprioception.

One large and as yet unmet treatment goal is modification of the underlying joint structure. Some studies suggest that disease progression may be modified by glucosamine sulphate, chondroitin sulphate, sodium hyaluronan, doxycycline, MMP inhibitors, bisphosphonates and calcitonin [89]. Disappointingly, it may be a while before a disease-modifying drug is available as cartilage remains the major focus of drug development, and yet cartilage has been shown to not be the direct cause of symptoms [90].

Conclusion

Given that the prevalence of OA in the population continues to rise, it poses a substantial public health burden. A number of risk factors for various joints have been identified. Of all the modifiable risk factors mentioned in this review, to date, only obesity and avoiding joint injury have sufficient evidence to support intervention. As structural lesions appear to be a cause of significant pain in OA sufferers, this presents a promising avenue for future therapeutic targeting. There are numerous methodologic challenges in attempting to study risk factors for OA, and therefore prevention of OA also remains challenging. There is a need for ongoing epidemiologic studies for the prevention of incident and progressive OA, as well as pain related to OA.

Conflict of interest

There are no competing interests.

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Osteoarthritis and Cartilage

Loss of anterior cruciate ligament integrity and the development of radiographic knee osteoarthritis: a sub-study of the osteoarthritis initiative

V.L. Johnson † ‡, C.K. Kwoh §, A. Guermazi ‖, F. Roemer ‖ ¶, R.M. Boudreau §, T. Fujii §, M.J. Hannon §, D.J. Hunter † *

† Institute of Bone and Joint Research, University of Sydney, Australia
‡ School of Medicine, University of Sydney, Australia
§ University of Pittsburgh, Pennsylvania, USA
‖ Boston University School of Medicine, Boston, MA, USA
¶ Klinikum Augsburg, Augsburg, Germany

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SUMMARY

Introduction: The aim of this study was to determine whether loss of ACL integrity in an older cohort precedes the onset of radiographic OA (ROA).
Methods: Participants in this nested case–control study were selected from the Osteoarthritis Initiative (OAI) study who had risk factors for OA development but did not have ROA (Kellgren–Lawrence grading (KLG) of 0 or 1) in both knees at baseline. The MRIs were assessed for the presence of ACL tears. Case knees were defined by the development of ROA on knee radiographs between the 12 and 48 month visits. Their radiographs were assessed at P0 (time of onset of radiographic knee OA), 1 year prior to P0 (P-1) and at baseline. Controls were selected from amongst those who did not develop incident ROA and were matched to cases.
Results: 355 persons who developed ROA were matched to 355 controls. No relationship between loss of ACL integrity and incident ROA was found at any assessment time point. Odds ratios (OR) for baseline, 1 year prior to incident ROA (P1) and at point of occurrence of incident ROA (P0) were 2.00 (0.66–6.06), 2.5 (0.76–8.24) and 2.75 (0.85–8.88) respectively. A significant risk of incident ROA was found in participants who had a history of knee injury with an OR of 1.51 (1.05–2.16).
Conclusion: Loss of ACL integrity does not confer a significantly increased risk of incident ROA in an older adult cohort. In contrast, a history of knee injury was associated with an increased risk of incident ROA.

Introduction

Despite the introduction of biomechanical training programs in schools and elite sporting organisations[1,2] the knee remains one of the most commonly injured joints. In the context of osteoarthritis (OA) the most important injuries are those resulting in the rupture of the anterior cruciate ligament (ACL), which is responsible for restraint of anterior tibial translation, as it is often accompanied by damage to the articular cartilage, subchondral bone, menisci and collateral ligaments.

The risk of ACL rupture is higher in adolescents and up to 70% higher in high-risk sports than in the general population[3]. ACL rupture is strongly linked to the subsequent development of OA with a substantial percentage of patients showing OA changes and functional disability as early as 10 years after the initial injury[3,4]. It is thought to account for up to 15% of a person's risk of developing knee OA however it typically occurs in adolescents and young adults[3]. At the present time, no study has established whether a similar relationship between ACL injury and incident OA exists in an older adult cohort. ACL deficiency causes increased translational shear force on the cartilage and in combination with age, is one of

* Address correspondence and reprint requests to: D.J. Hunter, Institute of Bone and Joint Research, University of Sydney, Australia.
E-mail address: David.Hunter@sydney.edu.au (D.J. Hunter).

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the strongest predictors of OA[5], this could confer an increased risk of OA development.

The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is not known. Persons with ACL tears have been shown to be at an increased risk for cartilage loss[6], meniscal degeneration, osteophyte formation and bone marrow lesions (BMLs)[7] with the pattern of damage being consistent with the initial location of osteochondral injury of an ACL rupture in the lateral tibiofemoral compartment[8].

Although radiographic features such as joint space narrowing and the presence of osteophytes define the presence of radiographic OA (ROA), magnetic resonance imaging (MRI) may improve the assessment of early disease development and progression. MRI has shown a higher specificity and sensitivity for the assessment of joint morphology[9] and the diagnosis of post-traumatic degenerative changes[10,11]. Thus MRI may improve the assessment of early disease development preceding the development of either joint space narrowing or osteophyte formation on a plain radiograph. At this point the underlying structural changes that predate the development of ROA remain under examined[12].

Therefore, the aims of this study were to identify whether a similar relationship between ACL injury and radiographic knee OA that as been reported elsewhere in an adolescent cohort[3,4] also exists in an older adult cohort. Furthermore, whether a history of knee injury in an older adult cohort results in an increased risk of incident radiographic knee OA.

Patients and methods

Study design and subjects

The study participants were selected from the Osteoarthritis Initiative (OAI), which is a multi-centre, 10-year, longitudinal, prospective observational cohort study designed to identify biomarkers and risk factors for knee OA causation and progression.

4,796 study subjects underwent a detailed assessment annually, including physical examination, and interview using self-reported measures, such as joint pain and disability as well as knee MRIs and radiographs. Covariates including body mass index, muscle strength, and physical activity were collected in tandem with the outcome assessments. Details of subject inclusion and exclusion have been described elsewhere[13] however, individuals with bilateral end-stage knee OA, knee arthroplasty, or bilateral radiographs with Kellgren and Lawrence (KLG) grade 4, and inflammatory arthritis were excluded from the study population.

The individuals for this sub-study were selected from those who did not have bilateral radiographic knee OA at enrolment (i.e., KLG of 0 or 1). Some individuals who were selected to this cohort had frequent knee pain but did not have radiographic tibio-femoral OA at enrolment[14].

Cases and controls

Cases were defined as study participants who had at least one knee that developed incident ROA; i.e., the first occurrence of radiographic findings compatible with OA (KLG of $\geq$2 on the PA view)[15] from baseline to the 48 month visit. The first occurrence of ROA was called time point P0. The 12 month time point before ROA was called P1.

The same number of controls were selected from the participants who did not develop incident ROA during the study period and matched to cases knees on sex, age within 5 years and contralateral knee status (i.e., KL = 0,1, or 2+ in the other knee). Each case was matched to a sample of those who are at risk at the time of case occurrence, whether this be at 12, 24, 36 or 48 months of follow-up. Both cases and controls were KLG 0 or 1 at baseline and the case knee had to display no radiographic signs of incident OA to be eligible as a control.

Radiographs

Radiography of both knees was performed in all subjects. The radiographs of knees were assessed for their KLG[16]. Radiographs acquired at baseline, 12, 24, 36 and 48-month visits were read by the OAI central readers for KLG of $\geq$2 (case definition)[16] on the postero-anterior (PA) knee radiographs.

A total of 355 participants who displayed KLG of 0 or 1 at baseline, went on to develop radiographic signs of knee OA at relevant time points (defined as KLG $\geq$2 on the PA fixed-flexion radiographs with incidence cases not having any definitive joint space narrowing).

MRI sequence parameters

MRI acquisition was performed using a 3 T MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites. Non-contrast enhanced MRIs of both cases and controls from enrolment and the visits prior to and when meeting case and control definitions, were read.

The MRI pulse sequence protocol included a coronal two-dimensional intermediate-weighted (IW) turbo spin-echo[17], sagittal three-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multiplanar reformations of the 3D DESS and sagittal IW fat saturated (FS) TSE sequences. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail[13].

The MRI Osteoarthritis Knee Score (MOAKS) system was used to assess the whole joint for structural changes compatible with knee OA[7]. MRI readings were performed by AG and FWR with 14 and 11 years experience in MRI semi-quantitative assessment respectively. Scores were entered directly into an electronic web-based database. All MRIs were read sequentially and un-blinded to time point, but blinded to case/control status. Inter-rater calibration and reliability-testing on a subset of MRI scans was performed for MRI reading quality control. Subsequently, on going surveillance for measurement drift was carried out by AG by re-reading 5% of the MRIs.

ACL tears

Sagittal and coronal views were used to detect the presence of an ACL tear at baseline and scored on a 0–2 scale (0 = normal, 1 = partial tear and 2 = complete tear). A tear was defined as complete when complete disruption of ACL fibres and ligament discontinuity were noted, whilst residual straight and tight ACL fibres in at least one-pulse sequence was defined as a partial tear. Since partial tears may change the joint biomechanics and thus the pattern of joint damage, partial and complete tears have been combined. Fig. 1 shows an example of an ACL tear that occurred between baseline and P0, as visualized on MRI. All MRIs were read by a single board-certified musculoskeletal radiologist, separate from the scoring of other joint features and blinded to the hypothesis being tested.

Selection of knees for inclusion

All incident knees were classified into one of five strata based on the baseline KLG status in both knees. Strata A was participants who had KLG = 0 for both knees. Strata B for KLG = 0 in one knee

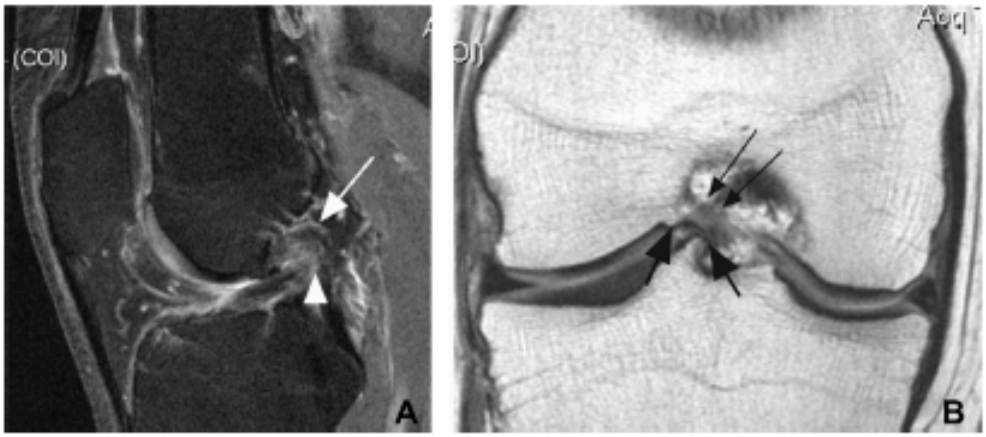

Fig. 1. Prevalent ACL tear in a 61-year-old male participant. A. Sagittal PS IW MR image shows complete disruption of ACL (arrowhead). Note also increased bowing of posterior cruciate ligament (arrow), an indirect sign of ACL damage and potential joint instability. ACL damage may be prevalent in osteoarthritis without recall of previous injury. B. Coronal IW image shows complete rupture of ACL with only remnant fibers visible (thin arrows). Likely etiology of non-traumatic ACL disruption in this case was chronic friction of tibial spine and femoral notch osteophytes. Note absence of osteophytes at the joint margins.

and KLG = 1 in the other. Strata C for KLG = 1 in both knees. Strata D for those with KLG = 0 in one knee and KLG≥ 2 in the other and strata E for participants who had KLG = 1 in one knee and KLG≥ to 2 in the other.

Assessment of joint injury

History of previous injury to the knee was evaluated at the enrolment visit by asking the participants whether they have ever injured their knee(s) badly enough to limit their ability to walk for at least 2 days.

Statistical analysis

Conditional logistic regression models were employed to model the relationships between the key predictors and OA. A GEE (general estimated equations) method with a robust sandwich estimator was used to account for the correlations between knees for cases of bilateral incident OA or two knees from the same individual used as controls.

The ACL tear predictors and their odds-ratios were modelled; the time point concurrent with incident ROA (P0), the time point 1-year prior to incident ROA (P1) and baseline.

Results

The demographics and baseline clinical parameters are listed in Table I. Sixty-six percent of the study population were women, the average age of the case subjects was 60.1 years with a standard deviation (SD) of 8.6, with the average age of the matched controls being 60.0 years with an SD of 8.4. The mean BMI was 28.9 kg/m^2 (SD 4.5) and 27.7 kg/m^2 (SD 4.4) for cases and controls, respectively and this difference was significant ($P = .0003$).

A total of 16 study participants demonstrated either a partial or complete ACL tear, of which 15 study participants had either partial or complete ACL tears at baseline. Of these 15 tears present at baseline, 14 ACLs were graded as partially torn (four controls and 10 cases) and one participant in the control group was graded as completely torn. The remaining ACL tear occurred in a participant in the case group who was noted to have partially torn their ACL at the P0 time point. The timing of onset of ROA (not timing of ACL tear) with the number of subjects who developed ROA at each time point is illustrated in Fig. 2. Of the 710 study participants, a history of knee injury was reported in 63 controls and 89 cases at baseline.

Table I
Baseline characteristics of the cases and controls in the study population

		Total ($N = 710$)		Controls ($N = 355$)		Cases ($N = 355$)	
		N	%	N	%	N	%
Participant Demographics							
Gender	**Male**	236	33.24	118	33.24	118	33.24
	Female	474	66.8	237	66.8	237	66.8
Mean Age		60.1 ± 8.5		60.0 ± 8.4		60.1 ± 8.6	
Mean BMI		28.3 ± 4.5		27.7 ± 4.4		28.9 ± 4.5	
Strata Class							
	A	126	17.75	63	17.75	63	17.75
	B	152	21.41	76	21.41	76	21.41
	C	166	23.38	83	23.38	83	23.38
	D	118	16.62	59	16.62	59	16.62
	E	148	20.85	74	20.85	74	20.85
Baseline Kellgren and Lawrence (grades 0/1)							
	0	266	37.46	133	37.46	133	37.46
	1	444	62.54	222	62.54	222	62.54
Injury at Baseline							
		152	21.41	63	17.75	89	25.07

Results of the effect of ACL tear and history of injury on the incidence of knee OA can be found in Table II. No significant relationship between radiographic incident OA and rupture of the ACL was found at any of the observed time points (P1 OR = 2.50, 95% CI = 0.76–8.24; P0 OR = 2.75, 95% CI = 0.85–8.88). Only in participants who reported having a history of knee injury at baseline (OR = 1.51, 95% CI = 1.05–2.16) was a significantly increased risk of developing incident radiographic knee OA found.

Discussion

The results presented show that, in an older adult cohort, an ACL tear is an infrequent event that does not appear to significantly predispose an individual to incident knee ROA.

Traumatic knee injuries involving ACL rupture are the most common form of knee injury and due to it's high incidence in adolescents[3,18], it has been widely studied due to its potential for the subsequent development of OA as well as functional disability as early as 10 years after the initial injury[3,4]. A review by Oiestad[17] reported a prevalence of knee OA of 13% for subjects who suffered from an isolated traumatic injury of the ACL. Our study also demonstrated that participants who reported a history of knee injury, or who had an observable injury at baseline testing conferred a significant risk of developing incident knee ROA.

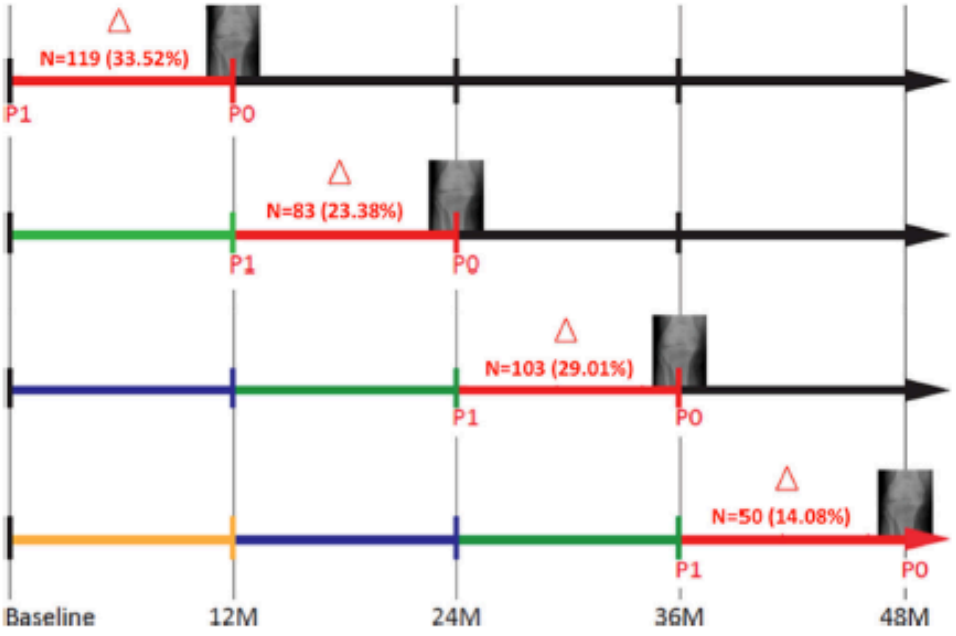

Fig. 2. Schema detailing the timing of onset of ROA with the number of subjects who developed ROA at that time point.

Table II
Conditional logistic regression analysis for occurrence of incident ROA due to ACL tears in the study population

	Total ($N = 710$)		Controls ($N = 355$)		Cases ($N = 355$)		OR	95% CI
	N	%	N	%	N	%		
ACL Tear at Baseline								
No Injury	695	97.89	350	98.59	345	97.18	1.00	
Partial Tear	14	1.97	4	1.13	10	2.82	2.00	0.66–6.06
Complete Tear	1	0.14	1	0.28				
ACL Tear Present 12 months prior to Radiographic Incidence (P1) $N = 660$								
No Injury	646	97.88	326	98.79	320	96.97	1.00	
Partial Tear	13	1.97	3	0.91	10	3.03	2.50	0.76–8.24
Complete Tear	1	0.15	1	0.30				
ACL Tear Present at Radiographic Incidence (P0) N = 670								
No Injury	655	97.76	331	98.81	324	96.72	1.00	
Partial Tear	15	2.09	4	0.90	11	3.28	2.75	0.85–8.88
Complete Tear	1	0.15	1	0.30				
Baseline Injury								
	152	21.41	63	17.75	89	25.07	**1.51**	**1.05–2.16**

Bold values represent the only numbers that reached significance.

However, whilst it has been well documented that a younger cohort have a significantly increased risk of developing knee OA post ACL injury, it has not been widely documented whether an ACL injury in older cohorts, in which OA is more prevalent, carries a similar risk. This study demonstrated that in an older cohort having a partial ACL tear, whether it is a partial or complete, does not lead to a statistically significantly increased risk of incident ROA. A similar result was found by the only other paper to have investigated this question. Amin *et al.*[19] found that a complete ACL tear did increase the risk for cartilage loss at the medial tibiofemoral compartments. However, following adjustment for the presence of medial meniscal tears there was no further increased risk for cartilage loss. Thus it was concluded that individuals with knee OA and an incidental complete ACL tear did not confer an increased risk for cartilage loss above that of what is mediated by meniscal pathology.

One potential reason for this difference has been suggested in a study by Hasegawa *et al.*[20] which identified degenerated ACLs in knees without cartilage degeneration. It was shown that inflammatory cells existed between collagen fibers within the ACL substance, regardless of the presence of cartilage degeneration. This indicated that an inflammatory process is driven by ACL intrinsic mechanisms that are linked explicitly with ageing. Therefore, these degenerative ligamentous changes may contribute to the increased fragility of the ligament thus predisposing it to tearing or rupture from minor trauma independent of the cartilage, osteochondral or meniscal changes associated with OA. These findings are particularly relevant to this study because where an ACL tear was observed on MRI in participants in this study they were not definitively linked to a prior significant injury, thus suggesting that many of these tears were degenerative in nature.

Another reason for the differences between these two populations could be due to the nature of the injury. In adolescents the majority of ACL injuries occur during sporting activities that involve pivoting and jumping. These injuries usually involve large impact forces and most often result in injury not only to the ACL but also to the meniscus and articular cartilage with a subsequent development of BMLs[4]. It is these large forces that are responsible for the majority of tissue damage[21]. It has been shown that occult osteochondral lesions of the posterolateral tibial plateau are seen on MRI in 80–90% of patients with an acute ACL injury suggesting that articular cartilage sustains a considerable impact at the time of injury[8]. Oiestad *et al.*[17] proposed that the prevalence of OA due to ACL rupture with concomitant meniscal damage might be as high as 40%.

Injury to the ACL in the elderly population would not require large forces when considering the aforementioned ligamentous degenerative changes. Without these large forces being imparted on the joint, there may be no associated injury to the meniscus or underlying articular cartilage at the time of ACL rupture. Thus it is likely that incidental tears to the ACL do not impact upon other joint tissues and as such do not contribute to the pathological processes of knee OA.

Limitations

The frequency of ACL tears in this study sample was smaller than previously described in the literature with one complete ACL tear and 15 partial ACL tears with a tear rate of 2.25% in the whole study population. Previous studies investigating ACL tears in individuals

with established knee ROA presented rates of ACL full-thickness tears ranging from 22 to 35%[6,22]. This decreased prevalence of ACL tears may be related to the selection factors used to define the 355 participants chosen from the OAI study to become part of this sub-study. The fidelity of MRI in ACL diagnosis has accuracy between 90% and 100% compared to knee arthroscopy, which is the gold standard[23,24], but is yet to be demonstrated in patients with knee OA. Such misclassification would bias towards a null result, so our findings may underestimate the true associations.

Having only 16 participants out of a sample size of 710 suffer from a complete or partial ACL tear makes this a small sample size. This would explain why the point estimate OR at baseline, P0 and P1 were substantial yet the 95% CI did not produce significance. Furthermore, MRI appears to be limited in the diagnosis of partial tears, and thus there is a possibility that other participants with partial tears may have been missed. Hence, these results need to be confirmed in a larger cohort.

Given concomitant ACL and meniscal tears/subluxation likely accelerate structural progression it would have been helpful to know about meniscal function and status. At the time of writing this data was not unfortunately available for inclusion.

Finally, the relationship between partial ACL tears and the development of incident OA is uncertain and not well documented. As the majority of tears observed in this study were rated as 'partial' comparisons between our study and with studies of complete tears are therefore of limited significance.

Conclusion

In summary, the loss of ACL integrity on MRI imaging may not confer a significantly increased risk of incident ROA in an older adult cohort. Our study only found that patients who had a history of knee injury had an increased risk of incident ROA. Further longitudinal research is required to corroborate these findings.

Author contributions

VLJ and DJH conceived and designed the study, supervised its conduct, drafted the manuscript and take responsibility for the integrity of the work as a whole, from inception to finish. CKK, AG, FR, RMB and MJH were also involved in the design and conduct of the POMA study. All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

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Competing interest

Drs. Johnson, Hunter, Boudreau, Fujii and Mr Hannon report no competing interest.

Ali Guermazi is President and co-owner of the Boston Core Imaging Lab (BICL), a company providing MRI reading services to academic researchers and to industry. He has provided consulting services to Novartis, Merck Serono, Sanofi-Aventis, TissueGene and Genzyme.

Frank Roemer is CMO and co-owner of the Boston Core Imaging Lab (BICL), a company providing MRI reading services to academic researchers and to industry. He has provided consulting services to Merck Serono.

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Does Age Influence the Risk of Incident Knee Osteoarthritis After a Traumatic Anterior Cruciate Ligament Injury?

Victoria L. Johnson,*† MBBS, BAppSci(Hons), Justin P. Roe,‡ MBBS, Lucy J. Salmon,‡ PhD, Leo A. Pinczewski,‡ MBBS, and David J. Hunter,*†§‖ MBBS, MSpMed, MScMed(ClinEpid), PhD
Investigation performed at the North Sydney Orthopaedic and Sports Medicine Centre, Sydney, Australia

Background: The development of radiographic knee osteoarthritis (OA) after an anterior cruciate ligament (ACL) rupture has long been studied and proven in the adolescent population. However, similar exhaustive investigations have not been conducted in mature-aged athletes or in older populations.

Purpose: To identify whether an older adult population had an increased risk of incident radiographic knee OA after a traumatic knee injury compared with a young adult population.

Study Design: Cohort study; Level of evidence, 3.

Methods: Patients with ACL ruptures who underwent primary reconstruction were enrolled in a prospective, longitudinal single-center study over 15 years. The adult cohort was defined as participants aged ≥35 years who had a knee injury resulting in an ACL tear, the adolescent-young cohort suffered similar knee injuries and were aged ≤25 years, and a third cohort of participants aged 26 to 34 years who suffered a knee injury was included to identify the existence of any age-related dose-response relationship for the onset of radiographic knee OA. A Kaplan-Meier survival analysis was employed to determine the occurrence of incident radiographic OA across the study populations at 2, 5, 10, and 15 years after reconstruction. Significance at each time point was analyzed using chi-square tests.

Results: A total of 215 patients, including 112 adolescents (mean age, 20.4 years; 50.9% female), 71 patients aged 26 to 34 years (mean age, 29.2 years; 42.3% female), and 32 adults (mean age, 40.2 years; 59.4% female), were assessed for International Knee Documentation Committee (IKDC) grading on knee radiographs. It was found that 53.0% and 77.8% of adults at a respective 10 and 15 years after reconstruction had an IKDC grade of B or greater compared with 17.7% and 61.6% of the adolescent-young cohort. Chi-square testing found that adults developed OA earlier than adolescents at 5 and 10 years after reconstruction ($P = .017$ and $P < .0001$, respectively). However, survival analysis did not demonstrate that adults were more likely to develop radiographic knee OA at 15 years after reconstruction compared with the adolescent-young cohort ($P = .4$).

Conclusion: The age at which an ACL injury is sustained does not appear to influence the rate of incident radiographic knee OA, although mature-aged athletes are likely to arrive at the OA endpoint sooner.

Keywords: knee; ACL injury; osteoarthritis; age

‖Address correspondence to David J. Hunter, MBBS, MSpMed, MScMed(ClinEpid), PhD, Kolling Institute, Royal North Shore Hospital, St Leonards, Sydney, Australia 2065 (email: david.hunter@sydney.edu.au).

*Institute of Bone and Joint Research, Kolling Institute of Medical Research, University of Sydney, Sydney, Australia.

†Sydney Medical School, University of Sydney, Sydney, Australia.

‡Mater Clinic, North Sydney Orthopaedic and Sports Medicine Centre, Sydney, Australia.

§Rheumatology Department, Royal North Shore Hospital, Sydney, Australia.

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A rupture of the anterior cruciate ligament (ACL) is a common cause of severe knee injuries, which affects physically active men and women as the ACL is essential for knee kinematics by functioning as the main restraint of anterior tibial translation and acts as an anterior-posterior stabilizer.[4] ACL injuries occur with an annual incidence of 81 per 100,000 persons aged between 10 and 64 years,[5] with the risk of ruptures highest among adolescents who participate in high-risk sports. As the majority of these injuries occur in a younger population, the long-term consequences of prolonged disability due to joint instability, meniscal and chondral surface damage, and thus subsequent osteoarthritis (OA) development mean that these injuries carry a large financial and health encumbrance caused by both pain and loss of physical functioning.[18] Traumatic lesions

to the ACL are a well-known risk factor for OA,[4,10] with radiographic changes suggestive of OA[6,10] having been reported as early as 10 years after the initial injury in up to 70% of young adults who sustained an injury to their ACL.[12,14,16] This equates to a risk of OA incidence up to 5 times greater when compared with cohorts that have never suffered a knee injury.[6]

The subsequent development of radiographic knee OA after an ACL rupture has long been studied and proven[5,6,10,14,16] in the adolescent population. However, similar exhaustive investigations have not been conducted in mature-aged athletes and in older populations.

Age is one of the strongest predictors of OA; however, the exact mechanism is poorly understood. A combination of changes including the capacity for joint tissues to adapt to biomechanical insults, biological changes such as cellular senescence, and a reduced capacity to adjust to biomechanical challenges are likely contributing factors.[3]

Knowledge of the course of development of cartilage damage after a knee ligament injury is required when new methods of treatment are to be evaluated and when disease development is to be compared with other populations with OA. This type of information is also helpful in adequately informing patients about their likely prognosis.

Therefore, the aims of this study were to identify whether an older adult population has an increased risk of incident radiographic knee OA after ACL reconstruction compared with an adolescent population and whether older adults are at an increased risk of developing more severe radiographic knee OA.

METHODS

Study Design and Participants

A total of 215 patients with ACL ruptures who underwent primary reconstruction with hamstring autografts between October 1993 and March 1996 were enrolled in this prospective, longitudinal single-center study over 15 years. Three study populations were selected. The adult cohort (cases) were defined as study participants who had a knee injury resulting in an ACL tear and aged $\geq$35 years. The adolescent-young cohort (controls) were study participants with a similar history of knee injuries and ACL tears and aged $\leq$25 years. An additional cohort of participants aged 26 to 34 years was included to check for the existence of any age-related dose-response relationship for the onset of radiographic knee OA.

Exclusion Criteria

Participants were excluded from this study if the injury to their ACL included any other associated ligamentous injury requiring surgical management, any pre-existing significant chondral damage or degeneration as seen on radiographs before surgery, prior meniscectomy, excision of one-third or more of 1 meniscus and no meniscal instability, preoperative abnormal radiological findings, an abnormality in the contralateral knee, patients seeking compensation for their injuries, and those who did not wish to participate in a research program.

A local independent ethics committee granted ethical approval. Participants with a new acute injury were assessed clinically and a diagnosis made on the basis of clinical findings including Lachman, pivot-shift, and instrumented laxity tests on both knees.

Knee Injury

All of the ACL injuries measured in this study were sustained while each of the participants were involved in high-impact sporting activities. The majority of injuries were sustained playing soccer, rugby union, rugby league, skiing, and netball.

Surgical Technique

All procedures were performed by author L.A.P. The technique was standardized for all patients. A 4-strand gracilis and semitendinosus tendon graft was used, and the tunnel diameter equaled the measured diameter of the graft (range, 6-9 mm).

The femoral tunnel was drilled before the tibial tunnel via the anteromedial arthroscopic portal, with the knee in maximal flexion, and positioned 5 mm anterior to the posterior capsular insertion at the 10:30 or 1:30 clock position depending on whether the index knee for a participant was right or left. The tibial tunnel was centered on a line between the anterior tibial spine and the posterior margin of the anterior horn of the lateral meniscus, half the graft's diameter lateral along that line. In all cases, fixation consisted of a 7 $\times$ 25–mm titanium cannulated interference screw (RCI; Smith & Nephew Endoscopy) for both femoral and tibial fixations. By 6 weeks, jogging in a straight line, swimming, and cycling were permitted. After 12 weeks, general strengthening exercises were continued. Return to competitive sports involving jumping, pivoting, or sidestepping was discouraged until 9 months after reconstruction and a successful return to a sport program had been completed.

ACL Graft Rupture

During the course of the study, 25 participants suffered a rupture of their ACL graft, and this was confirmed at the time of revision ACL reconstruction. The diagnosis of an ACL graft rupture was based on clinical findings of a positive pivot-shift examination and/or Lachman test result (grade $\geq$2). Participants who suffered a graft rupture and/or subsequent revision surgery remained in the study.

Injury to the Meniscus

A total of 100 participants suffered a concomitant injury to their meniscus at the time of the ACL rupture, as seen in

TABLE 1
Study Demographics[a]

	Total (N = 215)	Adolescent-Young Cohort (n = 112)	Participants Aged 26-34 y (n = 71)	Adult Cohort (n = 32)
Age, mean ± SD, y	30.0 ± 13.8	20.4 ± 3.2	29.2 ± 2.5	40.2 ± 4.5
Female sex	106 (49.3)	57 (50.9)	30 (42.3)	19 (59.4)
Injury to right knee	110 (51.2)	55 (49.1)	38 (53.5)	17 (53.1)
Injury to either meniscus	100 (46.5)	55 (49.1)	29 (40.8)	16 (50.0)
ACL graft rerupture	25 (11.6)	21 (18.8)	2 (2.8)	2 (6.3)

[a]Data are reported as n (%) unless otherwise indicated. ACL, anterior cruciate ligament.

Table 1. An injury to the meniscus was determined arthroscopically at the time of ACL reconstruction.

Radiographs

A radiographic assessment was conducted at 2, 5, 10, and 15 years postoperatively with weightbearing anteroposterior, 30° of flexion posteroanterior, lateral, and patellofemoral views. Radiographs were classified according to the International Knee Documentation Committee (IKDC) guidelines as follows: A, normal; B, minimal changes but detectable joint space narrowing; C, moderate changes and joint space narrowing of up to 50%; and D, severe changes and more than 50% joint space narrowing. The worst grade in any compartment determined the overall IKDC radiographic grade. For the purposes of this study, radiographic OA was defined as an IKDC grade of B or greater.

Statistical Analysis

Statistical analyses were performed using SPSS software. A Kaplan-Meier survival analysis was employed to determine the occurrence of incident radiographic OA in all 3 study populations and to model the relationships between the key predictors (IKDC radiographic scoring) and OA, concurrent with each of the time points of 2-, 5-, 10-, and 15-year postoperative follow-up. The results were then plotted in a survival curve to determine if a dose-response relationship existed between age and the incidence of radiographic OA. The survival curves of each study population were compared using a Wilcoxon log-rank test. Chi-square tests were then used to compare the incidence of radiographic OA at each of the follow-up time points. Statistical significance was set at .05.

RESULTS

The demographics and baseline clinical parameters are listed in Table 1. Forty-nine percent of the study population was female, and the mean (±SD) age of the adult cohort was 40.2 ± 4.5 years at the time of ACL reconstruction (range, 35-58 years), with the mean age of the adolescent-young cohort being 20.4 ± 3.2 years (range, 13-25 years). The right knee was injured in 53.1% of adults and 49.1% of adolescent-young participants. A concomitant meniscal tear was noted in 16 adult (50.0%) and 55 adolescent (49.1%) participants. The number of participants who presented with a reinjury to their ACL (ie, rupture of the ACL graft) was highest among the adolescent-young cohort, with 21 participants (18.8%) compared with 2 (6.3%) in the adult cohort (P = .09) and 2 (2.8%) in the cohort of participants aged 26 to 34 years (P = .001). Further to this, during the 15-year study period, 12 adolescents (10.7%), 5 adults (15.6%), and 7 participants aged 26 to 34 years (9.9%) suffered further meniscal injuries requiring surgical correction.

The breakdown of the IKDC radiographic grades at each time point is displayed in Table 2. Only 1 adult participant had radiographic features of OA at 2 years postoperatively. A higher percentage of adult participants developed radiographic OA at each of the 5-, 10-, and 15-year postoperative time points when compared with the adolescent-young cohort. At 5-year follow-up, 38.5% of adults had an IKDC radiographic grade of B as compared with only 7.8% of adolescents (P = .017). At 10- and 15-year follow-up, a respective 53.0% and 77.8% of adults had a radiographic IKDC grade of B or greater (P < .0001 and P = .06, respectively). In comparison, 17.7% and 61.6% of adolescents had an IKDC grade of B or greater at 10- and 15-year follow-up, respectively. Additionally, significance was not reached when combining grades A and B against grades C and D of the adult and adolescent-young cohorts at 15 years (P = .66).

The Kaplan-Meier survival analysis for the incidence of radiographic knee OA for the adult, adolescent-young, and additional cohorts is displayed in Figure 1 and Table 3. Two years after surgery, adults had a survival estimate of 0.97 (95% CI, 0.82-1.00) against the adolescent participants of 1.00 (95% CI, 0.96-1.00). Adult participants had survival estimates of 0.84, 0.69, and 0.19, respectively, while adolescent-young participants had estimates of 0.96, 0.89, and 0.48 at 5, 10, and 15 years after surgery, respectively. While it appeared from the survival estimates that adults were more likely to develop radiographic OA, log-rank analysis found no statistical significance between the 2 curves (P = .4).

Chi-square testing showed that only at 5 and 10 years after reconstruction did the difference in OA incidence between the adult (38.5%) and adolescent-young cohorts (7.8%) reach significance (P = .017 and P <

TABLE 2
IKDC Grading Throughout the Study[a]

	Radiographic View				
	Medial	Lateral	Patellofemoral	Overall IKDC Grade[b]	*P* Value[c]
2-y follow-up					
Adults (not assessed: n = 15)					.73 (adults vs adolescent-young)
A	16 (94.1)	17 (100.0)	17 (100.0)	16 (94.1)	
B	1 (5.9)	—	—	1 (5.9)	
C	—	—	—	—	
D	—	—	—	—	
Adolescents (not assessed: n = 36)					**.004** (adolescent-young vs 26-34 y)
A	69 (100.0)	69 (100.0)	69 (100.0)	76 (100.0)	
B	—	—	—	—	
C	—	—	—	—	
D	—	—	—	—	
26-34 y (not assessed: n = 28)					.4 (26-34 y vs adults)
A	35 (81.4)	40 (93.0)	40 (93.0)	38 (88.4)	
B	6 (14.0)	1 (1.9)	1 (1.9)	5 (11.6)	
C	—	—	—	—	
D	—	—	—	—	
5-y follow-up					
Adults (not assessed: n = 19)					**.017** (adults vs adolescent-young)
A	9 (64.3)	11 (84.6)	12 (92.3)	8 (61.5)	
B	5 (35.7)	2 (15.4)	1 (7.7)	5 (38.5)	
C	—	—	—	—	
D	—	—	—	—	
Adolescents (not assessed: n = 61)					**.04** (adolescent-young vs 26-34 y)
A	49 (96.1)	50 (98.0)	51 (100.0)	47 (92.2)	
B	2 (3.9)	1 (2.0)	—	4 (7.8)	
C	—	—	—	—	
D	—	—	—	—	
26-34 y (not assessed: n = 28)					.53 (26-34 y vs adults)
A	34 (81.0)	39 (92.9)	41 (97.6)	33 (78.6)	
B	8 (19.0)	3 (7.1)	1 (2.4)	8 (19.0)	
C	—	—	—	—	
D	—	—	—	—	
10-y follow-up					
Adults (not assessed: n = 15)					**<.0001** (adults vs adolescent-young)
A	9 (52.9)	14 (82.4)	15 (88.2)	8 (47.1)	
B	7 (41.2)	3 (17.6)	2 (11.8)	8 (47.1)	
C	1 (5.9)	—	—	1 (5.9)	
D	—	—	—	—	
Adolescents (not assessed: n = 53)					>.999 (adolescent-young vs 26-34 y)
A	50 (84.7)	54 (93.1)	58 (100.0)	48 (82.3)	
B	9 (15.3)	4 (6.9)	—	1 (17.7)	
C	—	—	—	—	
D	—	—	—	—	
26-34 y (not assessed: n = 16)					.54 (26-34 y vs adults)
A	40 (72.7)	50 (90.9)	50 (90.9)	39 (70.9)	
B	12 (21.8)	4 (7.3)	5 (9.1)	14 (25.5)	
C	2 (3.6)	1 (1.8)	—	2 (3.6)	
D	—	—	—	—	
15-y follow-up					
Adults (not assessed: n = 5)					.06 (adults vs adolescent-young)
A	8 (29.6)	18 (66.7)	15 (55.6)	6 (22.2)	
B	15 (55.6)	9 (33.3)	12 (44.4)	17 (63.0)	
C	4 (14.8)	—	—	4 (14.8)	
D	—	—	—	—	
Adolescents (not assessed: n = 26)					.65 (adolescent-young vs 26-34 y)
A	39 (45.3)	53 (61.0)	60 (69.0)	33 (38.4)	
B	41 (47.7)	31 (35.6)	25 (28.7)	43 (50.0)	
C	6 (7.0)	2 (2.3)	1 (1.1)	8 (9.3)	
D	—	1 (1.1)	1 (1.1)	2 (2.3)	

(continued)

TABLE 2
(Continued)

	Radiographic View				
	Medial	Lateral	Patellofemoral	Overall IKDC Grade[b]	*P* Value[c]
26-34 y (not assessed: n = 15)					.15 (26-34 y vs adults)
A	21 (37.5)	35 (62.5)	37 (66.1)	20 (35.7)	
B	26 (46.4)	19 (33.9)	18 (32.1)	27 (48.2)	
C	9 (16.1)	2 (3.6)	1 (1.8)	9 (16.1)	
D	—	—	—	—	

[a]Data are reported as n (%) unless otherwise indicated.
[b]Radiographs for some participants were only assessed for an overall International Knee Documentation Committee (IKDC) grading, and the region of osteoarthritis occurrence (ie, specific to the medial, lateral, or patellofemoral compartments) was not specified. IKDC grades are as follows: A, normal knee with no features of radiographic osteoarthritis; B, minimal changes and barely detectable joint space narrowing; C, moderate changes and joint space narrowing of up to 50%; and D, severe changes and more than 50% joint space narrowing.
[c]Chi-square *P* value for overall IKDC grading. Bolded values indicate statistically significant between-group difference.

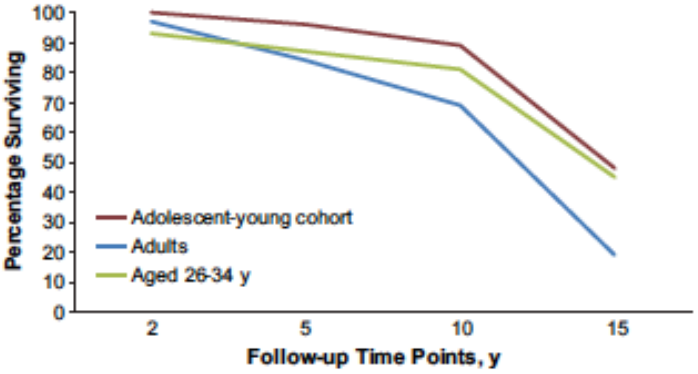

Figure 1. Schema of survival analysis detailing the onset of knee radiographic osteoarthritis. Log-rank analysis showed no difference between the adult and adolescent survival curves ($P = .4$). Chi-square analysis showed that only at 5 years after surgery did the difference between adults and the adolescent-young cohort reach statistical significance ($P = .017$).

.0001, respectively). This trend did not continue, however, as at 15 years after reconstruction, the difference between the 2 cohorts (77.8% vs 61.6%, respectively) was no longer significant ($P = .06$).

Additionally, as displayed in Table 2, it was found that a greater proportion of adults (70.4%), the adolescent-young cohort (54.7%), and those aged 26 to 34 years (62.5%) developed OA (IKDC grading of B or greater) in the medial compartment compared with the lateral compartment at 15 years after reconstruction. OA in the lateral compartment was only recorded in approximately one-third of each of the adult (33.3%), adolescent-young (39.0%), and 26- to 34-year (37.5%) cohorts. Patellofemoral OA was also noted in approximately one-third of all participants (adults, 44.4%; adolescent-young cohort, 30.9%; 26- to 34-year group, 33.9%).

Participants aged 26 to 34 years were included in the survival analysis to see if an age-related dose-response relationship was evident. Again, significance was reached only at 2 and 5 years after reconstruction between participants aged 26 to 34 years and the adolescent-young cohort ($P = .004$ at 2 years and $P = .04$ at 5 years) (Table 2). At no point did the participants in the 26- to 34-year group reach significance with the adult cohort using chi-square testing. At 15 years after reconstruction, there was no significant difference when comparing the survival curves of any of the 3 cohorts for the incidence of radiographic knee OA. Wilcoxon log-rank testing produced *P* values of .97 and .37 when comparing the 26- to

TABLE 3
Kaplan-Meier Survival Analysis for the Study Cohorts

	Participants Who Developed Knee Osteoarthritis					
	Adolescent-Young Cohort (n = 112)		26-34 y Cohort (n = 71)		Adult Cohort (n = 32)	
	No. of Patients	Probability Estimate (95% CI)	No. of Patients	Probability Estimate (95% CI)	No. of Patients	Probability Estimate (95% CI)
2 y after surgery	0	1.00 (0.96-1.00)	5	0.93 (0.88-0.98)	1	0.97 (0.82-1.00)
5 y after surgery	4	0.96 (0.91-0.99)	4	0.87 (0.83-0.96)	4	0.84 (0.66-0.94)
10 y after surgery	8	0.89 (0.82-0.94)	5	0.81 (0.77-0.92)	5	0.69 (0.50-0.83)
15 y after surgery	46	0.48 (0.39-0.58)	27	0.45 (0.49-0.69)	16	0.19 (0.07-0.37)

34-year cohort to the adult cohort and adolescent-young cohort, respectively.

DISCUSSION

The results presented show that adults who injure their ACL do not have an increased risk of OA at 15 years after a knee injury when compared with the adolescent-young population. This study found that while adults developed knee OA earlier than the adolescent-young cohort, the difference between the cohorts was no longer significant by 15-year follow-up. Further to this, the pattern of joint damage for all participants regardless of age followed a predominantly medial tibiofemoral pattern.

An acute ACL injury is associated with significant changes in bone curvature that are measurable within 3 months of the injury, leading to reduced congruency of joint surfaces and higher stresses on the articular tissues during activity.[8] Such a disruption to articular surfaces and other joint structures such as the meniscus and subchondral bone plate leads to joint instability and is a primary reason why traumatic knee injuries have been widely studied in the adolescent-young cohort, because of the strong potential for OA development and earlier onset of functional disability.[10]

Our results support previous studies investigating the relationship between adolescent athletes who rupture their ACL and the incidence of radiographic knee OA. Studies focusing on soccer players found that 12 years after an ACL injury, 41%[17] and 51%[12] of men and women exhibited radiographic knee OA, respectively. None of these participants were assessed to have OA in their noninjured contralateral knee. A review by Lohmander et al[10] is in keeping with our results. This review suggested that 50% of patients who suffer a traumatic ACL injury develop OA later in life. Recent data from the Osteoarthritis Initiative also showed that a recent knee injury, independent of age, was associated with an increased rate of knee OA.[2]

The only other study to have investigated potential differences in OA incidence among mature-aged and adolescent athletes was a retrospective, cross-sectional study by Roos et al,[16] which found that athletes aged >30 years with an isolated ACL injury developed incident radiographic knee OA, on average, about 10 years after the initial trauma. The incidence of radiographic knee OA was similar to those athletes aged <30 years who injured their ACL. Thus, there was no significant difference between the two cohorts ($P = .067$).

Overall, our study produced similar results that while active adults who injured their ACL developed radiographic knee OA initially at a faster rate than their adolescent-young counterparts, this difference was no longer apparent at 15 years after surgery as the adolescent-young cohort produced the same prevalence of knee OA as the adult cohort. Interestingly, studying the histopathology of ACL fibers throughout the aging process has produced results that suggest that an older knee would be at a higher risk of incident OA development after an injury. Hasegawa et al[7] found that intrinsic primary changes in the extracellular matrix, such as an increase in inflammatory cells within the collagen fibers of the ACL, increase the fragility of the ligament and by extension may cause ACL mechanical failure. Additionally, analysis of synovial fluid has shown that within days after a joint injury, there is an increase in turnover of the cartilage proteoglycan aggrecan and type II collagen, which may persist for years after the injury.[9,11] These marked cellular changes within the matrix of the ACL and other joint structures make the ligament vulnerable to injuries. Aging contributes to passive laxity in the ACL,[1] with Driban et al[2] establishing that older patients were at risk of a rapid cascade toward joint failure occurring in less than 1 year after suffering a traumatic injury to their ACL.

As knee trauma represents one of the primary causes of knee OA, when combined with altered ligament morphological characteristics due to the natural aging process, theoretically, this will place an aged, injured knee at an increased risk of developing incident radiographic knee OA earlier than an adolescent who injures his or her ACL. One of the primary reasons why our results are not reflective of these studies might be because of a low number of participants in the adult cohort who injured their knee and had radiographs performed at each time point. It was demonstrated that at 5 and 10 years after reconstruction, there was a significant difference between adolescents and adults, but this trend did not continue past this time point. This study was underpowered; had fewer participants drop out across each follow-up point it would have been interesting to see if this trend continued at 15 years after reconstruction.

An isolated ACL injury is uncommon, so it is also important to note that some participants in this study suffered concomitant meniscal injuries while others sustained further injuries such as an ACL graft rupture after reconstruction. An injury to the meniscus was common among all 3 study populations, while an ACL graft injury was more common among the adolescent-young cohort presumably because this cohort is more likely to return to sport after rehabilitation of their initial injury. Patients who suffer a meniscal injury at the time of an ACL injury are at a further increased risk of developing radiographic knee OA later in life than a patient with an isolated ACL tear.[2] Similarly, it is thought that a second traumatic injury to the knee causing an ACL graft rupture may also increase the risk of OA incidence, above that of a patient with a single traumatic event.[13]

Limitations

This study highlights the importance of knee injuries in the incidence of knee OA among 2 separate cohorts but does have a few limitations. The sample size of the adult population was smaller than those in previous studies investigating similar relationships, potentially underpowering the conclusions that can be gleaned from these data. Thus, while there do appear to be higher rates of OA in adults than in the adolescent-young cohort, this does not reach statistical significance.

A number of participants did not have radiographs performed at each of the nominated assessment time points.

For this reason, there was a high number of participants who were not assessed for radiographic changes at each time point throughout this study, and this could be the reason why at 10 and 15 years after reconstruction the difference between the 2 cohorts was no longer significant. Having more participants measured at each time point as well as additional time points in the future (ie, measurement at 20 years, 25 years) may have produced stronger results.

Magnetic resonance imaging (MRI) scans were not collected uniformly at any of the time points in this study. Preoperative MRI scans as well as MRI scans at each of the follow-up time points would have provided a more accurate description of the cartilage and subchondral bone changes that may have occurred throughout the course of this study.

Further, while the distinct age cohorts are reasonably well balanced for factors that may predispose to OA including female sex and meniscal injury, they were not matched for other factors that can influence the OA risk including body mass index and activity levels, which were not controlled for. Given that younger patients are likely to be more active and participate in high-impact sports when compared with adults, it is conceivable that this cohort is at a greater risk of initial injuries as well as reinjuries after return to sport, subsequently increasing their overall risk of radiographic incident knee OA.

Finally, this was a single-center study, and all operations were conducted by a single surgeon. For this reason, the generalizability of these findings to a larger population might be limited. The results of this study should thus be regarded as hypothesis generating and will require focused, long-term prospective investigations for confirmation of the results.

CONCLUSION

While adults who injure their ACL are at an increased risk of developing knee OA at a faster rate than adolescents, ultimately, anyone who injures their ACL, regardless of age, is at risk of developing knee OA within 15 years of the injury. However, the rate of incident OA among adults who injured their knee in this study is higher than the reported prevalence of approximately 1% of middle-aged adults having radiographic OA due to aging in the absence of other OA risk factors.[15] Injuries among the younger, physically active population have so often been the focus of study for the association of injuries and knee OA, but despite the results of this study, injuries among older adults still need significant attention. Degradation of the ACL extracellular matrix makes an aged knee vulnerable to injuries and thus may place this population at an increased risk of OA when combined with knee trauma.

It is imperative that the relationship between age, knee injuries, and OA incidence is studied with a more robust cohort in the future to identify whether older adults who injure their knee are at a potentially increased risk of joint instability, disability, and ultimately joint failure in a truncated time period. This would lead to prompt recognition of this at-risk population after injuries and the production of interventions to delay or prevent the onset of knee OA incidence.

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ORIGINAL ARTICLE

Comparison in knee osteoarthritis joint damage patterns among individuals with an intact, complete and partial anterior cruciate ligament rupture

Victoria L. JOHNSON,[1,2] Ali GUERMAZI,[3] Frank W. ROEMER[3,4] and David J. HUNTER[1,5]

[1]*Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney,* [2]*School of Medicine, University of Sydney, Sydney, New South Wales, Australia,* [3]*Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, Massachusetts, USA,* [4]*Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany, and* [5]*Rheumatology Department, Royal North Shore Hospital, Sydney, New South Wales, Australia*

Abstract

Aim: The aim of this study was to examine the difference in the pattern of articular damage in persons with either a partial anterior cruciate ligament (ACL) tear; a complete ACL tear or no ACL tear.

Methods: Our study included 600 individuals (of the 600 individuals, 25 with a partial, 12 with a complete ACL tear and 563 with no ACL tear) from the progression sub-cohort of the Osteoarthritis Initiative. Individuals had a mean age of 61.8 years (range 45–79 years). Chi-square tests were used to compare the location of meniscal pathology, bone marrow lesions (BMLs) and regional cartilage morphology between individuals with a partial or complete ACL tear, as seen on magnetic resonance imaging, as well as to a control group of 563 knees.

Results: Individuals with either a complete or partial ACL tear displayed predominantly medial tibiofemoral damage. Individuals with complete ACL tears were more likely to have cartilage lesions in the lateral posterior tibia ($P = 0.03$) and the medial anterior femur ($P = 0.008$) as well as BMLs in the medial posterior tibia ($P = 0.007$). However, no significant difference in meniscal morphology was found in either compartment. Individuals with no history of knee trauma or ACL injury displayed predominantly medial tibiofemoral compartment damage.

Conclusion: Individuals with prevalent ACL disruptions exhibited concomitant osteoarthritic changes in the medial tibiofemoral compartment, as seen on MRI. As the changes in joint tissues were predominantly located in the medial compartment, it is thought that these ACL tears may represent a manifestation of the overall disease process rather than the precipitant for osteoarthritis incidence.

Key words: anterior cruciate ligament, knee, knee injury, MRI, osteoarthritis.

INTRODUCTION

Injury to the anterior cruciate ligament (ACL) is common among young, active individuals and frequently results in joint instability.[1,2] The prevalence of knee injuries among active adolescents has been estimated to be 0.18%,[3] yet the prevalence of incidental ACL tears in the context of established radiographic knee osteoarthritis (OA) has been found to be as high as 35%, many of whom have no recollection of trauma.[4] The etiology and significance of an incidental ACL tear identified in those with knee OA remains unclear. Chondroid metaplasia, collagen fiber disorganization and mucoid degeneration of the ACL extracellular matrix may co-exist within the context of OA and can

Correspondence: Dr Victoria Johnson, Kolling Institute, Royal North Shore Hospital, St Leonards, 57/273A Fowler Road, Illawong, Sydney, NSW 2234, Australia.
Email: vjoh6545@uni.sydney.edu.au

occur in individuals without a history of knee trauma.[5] This suggests that the disruption of the ACL may signify degenerative failure of the ligament, as opposed to injury. Regardless of the mechanism, an ACL-deficient knee imparts greater translational shear forces on the cartilage and may represent a risk factor for accelerated cartilage destruction.[6]

The majority of the literature has focused on comparing the incidence and pattern of radiographic disease in individuals with a history of ACL rupture in adolescence to those individuals who develop radiographic OA but have no history of ACL injury.[7–11] At the present time there has been little investigation into whether an incidental ACL tear in individuals with established knee OA alters the pattern of synovial joint damage and no comparison in the location of bone marrow lesions (BMLs), cartilage morphology or meniscal derangement between individuals with either a complete or partial ACL tear. For this reason the risk of OA development and progression in knees with partial ACL tears is unknown. Partial tears may signify that a lower-impact force was imparted on the knee and thus results in less damage to surrounding structures leading to a different clinical prognosis for future OA development.

The aim of this study was to examine the pattern of articular damage in persons with partial or complete ACL tears by testing the following hypothesis: that complete ACL tears will be associated with increased cartilage loss, meniscal degeneration and display BMLs in the lateral tibiofemoral compartment, consistent with the predominant initial location of the osteochondral injury, when compared to individuals with partial ACL tears. An additional aim was to compare the radiographic pattern of damage of those individuals who have prevalent ACL tears to those individuals who have OA but have no ACL tears as seen on magnetic resonance imaging (MRI) to ascertain whether the damage to the ACL leads to different radiographic disease locations.

MATERIALS AND METHODS

Study design and participants

The study participants were selected from the Osteoarthritis Initiative (OAI) which is an ongoing 10-year, multi-center, longitudinal, prospective observational cohort study designed to identify biomarkers and risk factors for the development and progression of knee OA. The local institutional review boards approved the study protocol, amendments and informed consent documentation. The data for this research is available for public access at http://www.oai.ucsf.edu/. The specific datasets used are clinical dataset 0.1.1 and Image Release 0.B.1.

The OAI consists of a progression subcohort and an incidence subcohort. A total of 1389 participants with radiographic evidence of OA and symptoms of knee OA were recruited for the progression subcohort.

For the purposes of this study, a total of 600 participants were selected from the progression subcohort. The inclusion criteria required that both of the following criteria be present together in at least one knee at baseline:

1 frequent knee symptoms, defined as pain, aching or stiffness on most days of a month during the past year and
2 radiographic evidence of OA defined as definite tibiofemoral osteophytes (OARSI atlas grade ≥ 1) on X-ray.[12] Participants were excluded if they did not meet the criteria of radiographic knee OA defined by a centralized reading of Kellgren and Lawrence Grading (KLG) of a grade ≥ 2.

Of these 600 participants, 25 had a partial tear and 12 had complete ACL rupture at baseline as seen on MRI.

Assessment of joint injury

History of joint injury was evaluated at the enrolment visit by asking the participants whether they ever injured their knee(s) badly enough to limit their ability to walk for at least 2 days.

Radiographic assessment and knee selection

Radiographs of both knees were semi-quantitatively scored using KLG;[13] however, only one knee per participant was evaluated. The evaluated knee was selected on the evidence of symptomatic radiographic OA. Individuals with knee pain where chosen primarily due to the findings of the Framingham OA study[14] which showed that individuals with symptomatic knees without definite osteophytes have an increased risk of developing radiographic OA compared to knees without symptoms.

In patients with unilateral symptomatic radiographic OA, this knee was chosen for analysis, regardless of radiographic severity. For individuals with bilateral symptomatic radiographic OA, the knee with radiographic appearances that offered the greatest opportunity for detection of progression (KLG score of 2 or 3) was selected. If both knees had KLG scores of 2 or 3 then the knee with the greater extent of the following features was selected: greater anatomic axis varus

angulation, a minimum medial joint space width (JSW) of 2.0 mm, greater grade of medial joint space narrowing (JSN) (grades 1–3), the presence of any medial tibial or femoral osteophyte grade 2 with greater grade than lateral osteophytes or the presence of any medial tibial or femoral osteophyte.

Radiographic images acquired at baseline were read by the OAI central readers for KLG of ≥ 2 on the postero-anterior (PA) knee radiographs.

MRI sequence parameters

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites during the enrollment visit for each of the participants. The following joint structures were assessed: cartilage morphology, subchondral BMLs, meniscal status and meniscal extrusion. The MRI sequences used for each of the joint tissues are described below.

The MOAKS (MRI Osteoarthritis Knee Score) system was used to assess the whole joint for structural changes compatible with knee OA, including BMLs, cartilage morphology and meniscal derangement.[15] Inter-rater calibration and reliability testing on a subset of MRI scans was performed for MRI reading quality control. Ongoing surveillance for measurement drift was carried out by a musculoskeletal radiologist (AG) by rereading 5% of the MRIs.

Complete and partial ACL tears

Sagittal and coronal intermediate-weighted (IW) 2D Turbo Spin Echo (TSE) fat suppression views were used to detect the presence of an ACL tear at baseline and were scored as 0 = normal, 1 = partial tear and 2 = complete tear. A tear was defined as complete when there was complete disruption of ACL fibers with ligament discontinuity. Residual straight or tight ACL fibers in at least one-pulse sequence were defined as a partial tear. Signal alterations consistent with mucoid degeneration were excluded. Intraligamentous hyperintense signal changes without apparent thinning or discontinuity of the ligament consistent with mucoid degeneration of the ACL are not covered by the MOAKS scoring system and were not separately scored. Thus, mucoid degeneration was considered to be part of the 'normal' spectrum, as the focus was on ligamentous morphologic abnormalities consistent with partial or complete fiber disruption.

BMLs

A BML was defined as an irregular hyperintense signal in the subchondral bone, proximal to the epiphyseal line, as seen on sagittal IW TSE, time to recovery of 3200 ms, time to echo (TE) of 30 ms, slice thickness of 3 mm and field of view (FOV) of 160 mm. Sagittal dual echo in the steady state (DESS) sequences with slice thickness of 0.7 mm, 140 mm FOV were used to assist with localization of BMLs.

The BMLs were semi quantitatively evaluated for size and graded at the following locations: medial and lateral patella, medial and lateral trochlea, medial and lateral weight-bearing femur, medial and lateral tibia and subspinous tibia. The MOAKS scores were 0 = none, $1 \leq 33\%$ of the whole bone volume, 2 = 33–66% of the whole bone volume and $3 \geq 66\%$ of the whole bone volume. Only grade 3 BMLs in each of the subregions was included in the analysis.[15]

Menisci

The menisci were scored using the same sagittal IW TSE FS images; as well, the coronal 2D IW TSE images were used to score meniscal integrity. Meniscal damage was defined according to MOAKS as those menisci that showed disruption of the overall morphology and diffuse hyperintense signal in the body of the meniscus, based on a MOAKS score of > 2. Intra-mensical signal was not considered damage. Meniscal damage was evaluated in each of the following locations: the anterior horn, body and posterior horn of the medial and lateral menisci.

Cartilage morphology

Cartilage assessment of both the area size per subregion and percentage of subregion affected by full thickness cartilage loss was graded. The number of subregions with cartilage worsening (i.e., a higher score at 24 months *vs.* baseline) was defined separately for surface area and thickness. For both scores cartilage worsening was grouped into four levels and were defined as, 0 = no change, $1 \leq 10\%$, 2 = 10–75% and $3 \geq 75\%$ of the surface area of that region.

Statistical analysis

Chi-square tests were performed to examine whether individuals with a complete ACL tear exhibited a specific pattern of meniscal degeneration, BML location, bone marrow morphology and cartilage morphology in the index knee compared with the index knee of those individuals with a partial ACL tear. Significance was set at $P = 0.05$. Statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA).

Individuals with either a complete or partial ACL tear were then grouped together and these same

aforementioned variables were also compared to the index knee of those individuals who did not have an ACL tear.

RESULTS

The demographic characteristics of the overall study sample for participants with a complete, partial or no ACL tear can be seen in Table 1. In total, 356 participants (59% of the total study population) were female with the average age of the participants being 61.8 years old with a standard deviation (SD) of 9.4 years and a range of 45–79 years. The average age of females was 61.7 years (SD of 8.7 years and range 50–78 years) and the average age for men being 61.4 years (SD of 9.1 years and range 45–79 years). The mean body mass index (BMI) was 30.5 kg/m^2 (SD of 5.2). The left knee was picked as the index knee in 279 participants (46%). Of those with a complete ACL tear, a third were female, with an average age of 66 years (SD 7.5 years) and the average age of males being 69 years (SD 6.5 years). The average BMI of females was 32.0 (SD 5.9) and males 29.6 (SD 3.6). On average, 44% those with partial ACL tears were female, with an average age of 71 years (SD 9.5 years) and the average age of males being 65 years (SD 8.6 years). The average BMI of females was 32.4 (SD 7.2) and males 31 (SD 4).

Fifty-nine participants (9.8%) in our study sample did not meet the criteria of radiographic knee OA defined as KLG ≥ 2 by the centralized reading. The eligibility criteria used for the OAI progression subcohort were based on the identification of a definite tibiofemoral osteophyte at each OAI Clinical Center, and some disagreement in radiographic assessment with the adjudicated central reading of KLGs was expected. None of these participants had ACL tears.

A complete tear was present in 12 participants, while a partial tear was noted in 25 participants. Example radiographs of individuals with either a complete or partial ACL tear are exhibited in Figure 1, while Figure 2 provides radiographic examples of BML and meniscal and cartilage pathology. Thirty-five participants with an ACL tear reported a history of substantive previous knee injury; however, the exact time when this injury was suffered was not reported. There was no significant difference in meniscal derangement when comparing participants with partial and complete ACL tears (Table 2). Medial meniscal derangement was more common than lateral meniscal derangement, with the majority of damage located in the posterior and anterior horns of the medial meniscus. This pattern of damage was similar between both cohorts.

A different pattern of pathology was noted when comparing participants with either a complete or partial ACL tear and those participants who did not exhibit an ACL tear. Participants who did not have an ACL tear did not exhibit pathology as frequently in the anterior or posterior horns of the medial meniscus ($P = 0.003$ and 0.005) or the posterior horn of the lateral meniscus ($P = 0.008$) when compared to those participants who tore their ACL. However, they did have an increased risk of pathology in the central portion of the medial meniscus ($P = 0.001$).

Results for cartilage lesion locations can be seen in Table 3a and cartilage full-thickness lesion sizes in

Table 1 Study demographics

	All $n = 600$	Complete ACL tear $n = 12$	Partial ACL tear $n = 25$	No ACL tear $n = 563$
Gender, female, *n* (%)	356 (59.3)	4 (33.3)	11 (44)	341 (60)
Age, years, mean (SD)	61.8 (9.4)	56.9 (8.7)	64.5 (8.8)	61.5 (9.0)
BMI, mean (SD) kg/m^2	30.5 (5.2)	30.2 (4.3)	31.8 (5.6)	30.7 (4.8)
Index knee, left, *n* (%)	279 (46.4)	8 (66.7)	11 (44)	260 (46)
Kellgren and Lawrence grade of index knee (%)				
0	–	–	–	–
1	73 (12.2)	–	2 (8)	71 (12.6)
2	297 (49.5)	5 (41.6)	6 (24)	286 (50.8)
3	225 (37.5)	7 (58.4)	16 (64)	202 (35.9)
4	5 (0.8)	–	1 (4)	4 (0.7)
History of knee injury, yes for study knee, *n* (%)	215 (35.8)	12 (100)	23 (92)	180 (31.9%)

ACL, anterior cruciate ligament; BMI, body mass index.

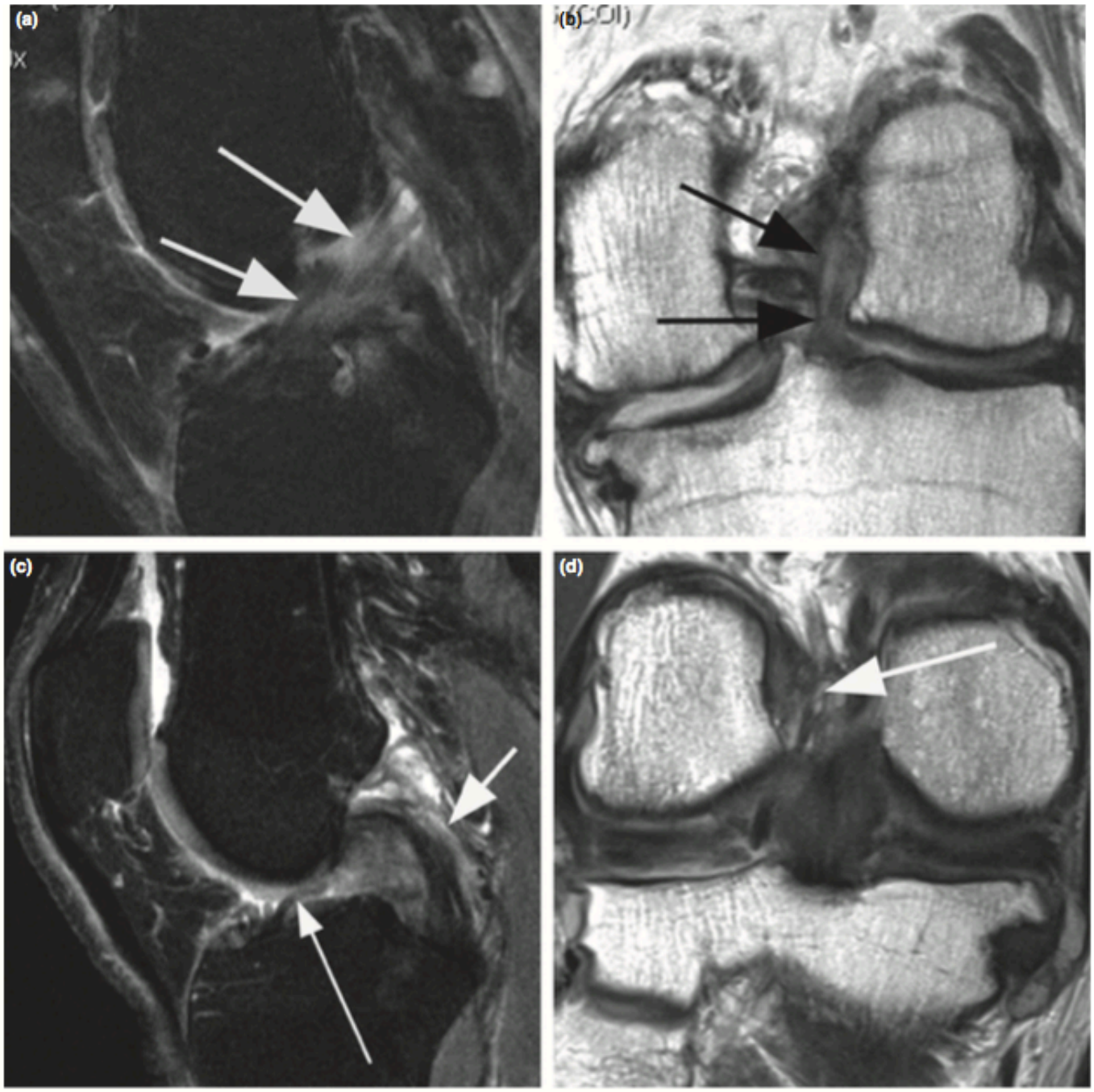

Figure 1 Examples of anterior cruciate ligament (ACL) pathology assessed using the MOAKS (Magnetic resonance imaging Osteoarthritis Knee Score) grading system. (a) Sagittal intermediate-weighted fat-suppressed image shows a thinned ACL with partial fiber disruption but remaining intact component (arrows). (b) Corresponding coronal intermediate-weighted image confirms these findings and also displays marked hyperintensity of remaining fibers (arrows). (c) A complete ACL tear is shown in this sagittal image. Only the tibial stump of the ligament can still be discerned (long arrow). Note intact posterior cruciate ligament (short arrow). (d) Corresponding coronal image shows proximal femoral remnant of ligament (arrow). There is complete fiber disruption in the intra-ligamentous portion of the ACL.

Table 3b. Participants with a complete ACL tear were more likely to have cartilage lesions located in the lateral posterior tibia ($P = 0.03$) and full thickness cartilage lesions in the medial posterior tibia ($P = 0.007$) when compared to those participants with a partial ACL tear. Those with a partial ACL tear were

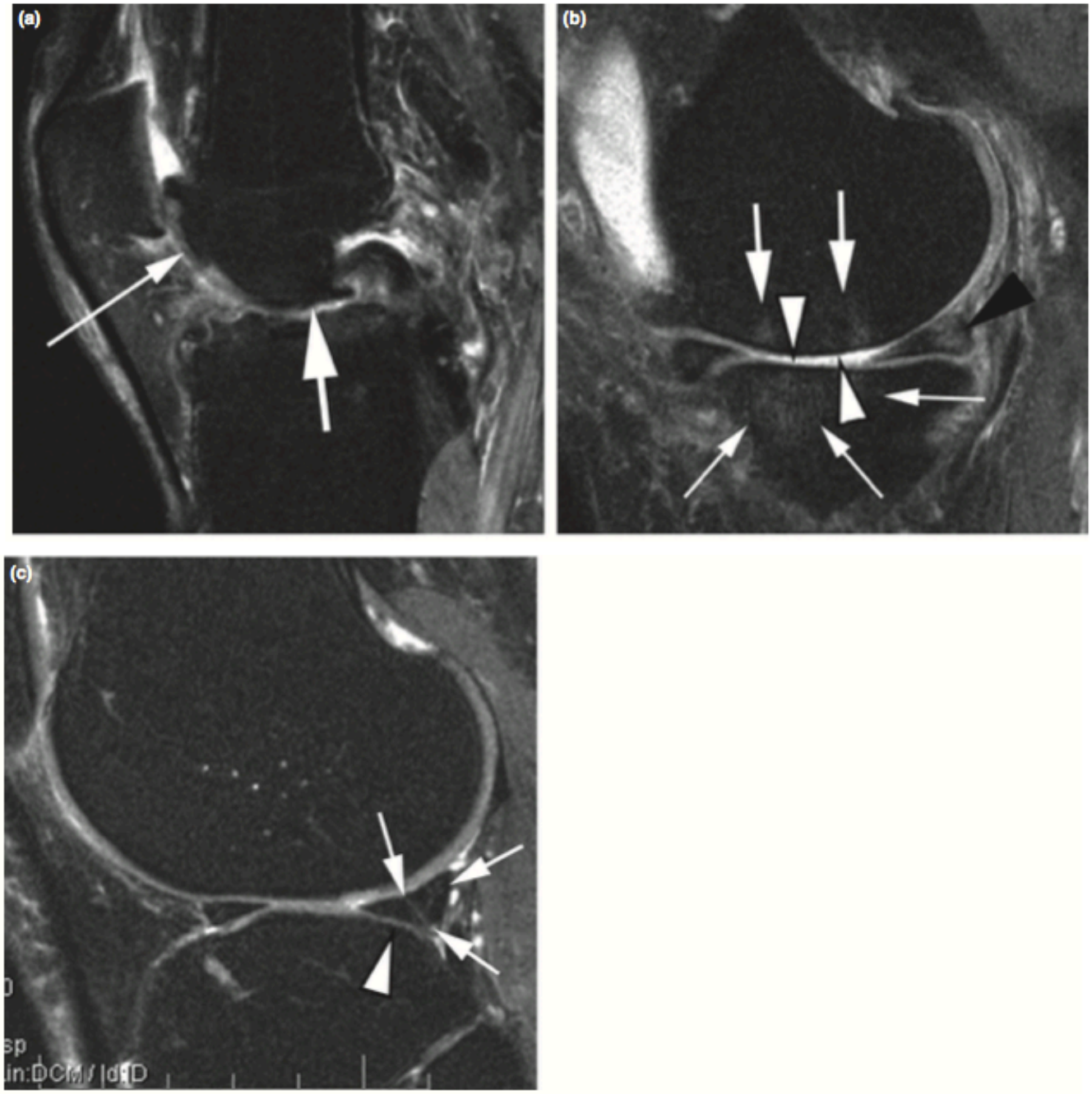

Figure 2 (a) Sagittal intermediate-weighted fat suppressed image shows absence of anterior cruciate ligament (ACL). There is associated full thickness cartilage loss at the medial femoral trochlea centrally (short arrow) and additional superficial cartilage damage further anteriorly of the trochlea (long arrow). (b) The same knee as in (a) exhibits marked full thickness cartilage loss at the central medial femur and tibia (filled arrowheads). In addition there are associated femoral (thick white arrows) and tibial (thin white arrows) bone marrow lesions. Note hyperintensity within the posterior horn of the medial meniscus reflecting mucoid degeneration (black arrowhead). (c) Another knee with a partial ACL tear exhibits a complex tear of the posterior horn of the lateral meniscus reaching the superior, inferior and posterior surfaces (white arrows). In addition there is superficial cartilage loss at the posterior lateral tibial plateau (filled arrowhead), a finding more commonly seen in those knees with prevalent ACL damage compared to those without.

Table 2 Meniscal pathology at baseline for participants with complete, partial and without ACL tears

	Complete ACL tear		Partial ACL tear		No ACL tear		*P*-values Complete *vs.* partial ACL tear	*P*-values Tear *vs.* no ACL tear
	n	%	*n*	%	*n*	%		
Medial anterior derangement								
No	9	75	23	92	551	98	0.3	**0.003**
Yes	3	25	2	8	12	2		
Medial body derangement								
No	2	17	11	44	393	70	0.14	**0.001**
Yes	10	83	14	56	170	30		
Medial posterior derangement								
No	1	8	8	32	307	55	0.22	**0.005**
Yes	11	92	17	68	256	45		
Lateral anterior derangement								
No	11	92	24	96	539	96	1.0	0.67
Yes	1	8	1	4	22	4		
Lateral body derangement								
No	11	92	25	100	523	93	0.32	0.5
Yes	1	8	–	0	40	7		
Lateral posterior derangement								
No	9	75	23	92	539	96	0.3	**0.008**
Yes	3	25	2	8	24	4		

ACL, anterior cruciate ligament. *P*-values in bold are significant.

more likely to have cartilage lesions in the medial anterior femur ($P = 0.008$).

Significant differences in almost all compartments of the tibia and femur for cartilage lesion locations and lesion sizes were demonstrated when comparing individuals with an ACL tear (combined partial and complete tears) and those without an ACL tear.

Significant differences in the location full thickness lesions (as seen in Table 3b) were seen in the lateral posterior tibia ($P = 0.01$), medial posterior tibia ($P = 0.02$), central medial tibia ($P = 0.001$), central lateral tibia ($P = 0.004$), medial posterior femur ($P = 0.004$), lateral central femur ($P = 0.02$) and medial central femur ($P = 0.001$). When considering cartilage lesion sizes (as seen in Table 3a) the subregions that failed to produce significant difference between those with an ACL tear and those without were the lateral central tibia, lateral posterior femur and the medial and lateral anterior femur.

As shown in Table 4, participants with partial ACL tears had more BMLs in the lateral anterior femur ($P = 0.038$) compared to those with complete ACL tears, while those with complete ACL tears had larger BMLs in the medial posterior tibia ($P = 0.007$). BMLs were more frequently seen in the medial patella, medial anterior and subspinous tibias of those individuals without an ACL tear.

DISCUSSION

Our study is the first to compare structural OA patterns between subjects with complete and partial tears of the ACL on MRI. Overall this study found no clear joint damage pattern differences between those individuals who suffered a complete rupture of their ACL and those who suffered only a partial tear of the ACL fibers. Both complete and partial ACL tears showed predominance for medial tibiofemoral damage with individuals who suffered a complete ACL rupture also exhibiting an increased risk of posterior tibial cartilage damage and BML formation.

A secondary aim of this study was to compare individuals with any type of ACL tear to individuals without an ACL tear. This study demonstrated a clear predisposition to medial tibiofemoral articular damage in persons with OA without an ACL tear seen on MRI.

Recently Eckstein *et al.*[7] quantitatively described medial tibiofemoral cartilage thickening occurring 5 years following ACL rupture. This increase in overall tibiofemoral joint cartilage thickness was also associated with localized cartilage thinning in the posterior subregions of the medial and lateral tibia. Similarly, our study found that individuals with a complete rupture of their ACL suffered significantly larger surface areas of cartilage loss and cartilage lesions in the posterior

Table 3 Cartilage morphology. Comparison of (a) cartilage surface area and (b) cartilage thickness loss between individuals with complete, partial and no ACL tears

Location	Complete ACL tear (%)				Partial ACL tear (%)				No ACL tear (%)				*P*-values	
	0	1	2	3	0	1	2	3	0	1	2	3	Complete *vs.* partial ACL tear	ACL tear *vs.* no tear
(a)														
Femur														
Medial anterior	75	–	17	8	28	12	60	–	45	12	42	1	**0.008**	0.19
Lateral anterior	60	8	32	–	52	4	28	16	63	4	29	4	0.5	0.54
Medial posterior	42	25	33	–	40	4	56	–	67	5	28	–	0.16	**0.002**
Lateral posterior	92	–	8	–	92	4	4	–	91	8	2	–	1.0	0.13
Medial central	16	8	68	8	12	24	72	4	35	16	45	4	0.64	**0.002**
Lateral Central	67	8	25	–	56	28	16	–	84	12	4	–	0.44	**0.001**
Tibia														
Medial anterior	75	–	25	–	60	–	40	–	84	1.7	14	0.3	0.48	**0.025**
Medial posterior	50	–	50	–	92	4	4	–	91	8	1	–	0.07	**0.001**
Lateral posterior	25	–	75	–	60	12	28	–	65	8	27	–	**0.03**	**0.006**
Medial central	34	–	50	16	24	–	68	8	55	2	41	2	0.52	**< 0.001**
Lateral central	75	–	25	–	72	12	16	–	76	10	14	–	0.52	0.55
(b)														
Femur														
Medial anterior	92	–	–	8	84	4	16	–	85	5	10	–	0.27	0.31
Lateral anterior	92	–	8	–	60	8	24	8	76	4	19	1	0.34	0.56
Medial posterior	66	25	9	–	88	4	8	–	95	3	2	–	0.12	**0.004**
Lateral posterior	100	–	–	–	100	–	–	–	98	2	–	–	1.0	0.95
Medial central	33	42	25	–	40	20	40	–	83	8	9	–	0.37	**0.001**
Lateral central	92	8	–	–	80	12	8	–	97	3	–	–	0.81	**0.02**
Tibia														
Medial anterior	100	–	–	–	96	4	–	–	96	2	2	1	1.0	0.39
Medial posterior	66	–	34	–	100	–	–	–	99	–	1	–	**0.007**	**0.02**
Lateral posterior	66	8	26	–	88	4	8	–	91	4	5	–	0.3	**0.01**
Medial central	58	17	25	–	56	16	28	–	87	7	6	–	0.99	**0.001**
Lateral central	75	16	8	–	84	12	4	–	95	3	2	–	0.68	**0.004**

ACL, anterior cruciate ligament. *P*-values in bold are significant.

medial and lateral tibia. To date the precise mechanisms involved in the observed thickening and thinning of joint cartilage following ACL rupture are not well understood. Perhaps the answer lies in the change of knee biomechanics following ACL rupture. Altered tibiofemoral cartilage contact biomechanics have been described following rupture of the ACL with the location of maximum cartilage contact deformation on the tibial plateau becoming more posterior and lateral. This shift in the area of cartilage contact during weight bearing results in an increase in the magnitude of cartilage contact deformation and causes increased loading of areas that were not conditioned to constant load prior to the loss of the ACL.[10,16,17]

Adolescent cohorts with ACL-deficient knees have an increased tibial internal rotation and increased posterior translation throughout gait.[17] Thus, changes to the biomechanical functioning of the knee secondary to a complete loss of ACL integrity might be the primary reason why complete rupture of the ACL may result in greater cartilage thinning of the posterior tibia when compared to only a partial ACL tear, as a partially intact ACL would still be able to provide some structural support and prevention of translational forces for the injured knee. This suggests that in the long term, individuals who tear their ACL completely may be exposed to more severe knee OA. This will ultimately lead to reduced functionality and greater knee pain. It would be interesting to see if longitudinal studies comparing complete and partial ACL tears support this proposition.

The posterolateral tibia is exposed to strong compression forces during a rupture of the ACL. These forces are

Table 4 Size and location of BMLs in participants with complete and partial ACL tears and in participants without ACL tears

Location	BML size	Complete ACL tear		Partial ACL tear		No ACL tear		*P*-values Complete *vs.* partial tear	*P*-values Tear *vs.* no tear
		n	%	*n*	%	*n*	%		
Lateral anterior femur	0	12	100	14	56	400	71	**0.038**	0.53
	1	–	–	6	24	68	12		
	2	–	–	4	16	71	13		
	3	–	–	1	4	24	4		
Medial anterior femur	0	10	83	18	72	412	73	1.0	0.92
	1	3	17	6	24	130	23		
	2	–	–	1	4	14	3		
	3	–	–	–	–	7	1		
Lateral posterior femur	0	12	100	25	100	543	96	1.0	0.95
	1	–	–	–	–	12	2.8		
	2	–	–	–	–	4	0.7		
	3	–	–	–	–	3	0.5		
Medial posterior femur	0	9	75	20	80	472	84	0.83	0.47
	1	2	17	4	16	75	13		
	2	1	8	1	4	13	2.5		
	3	–	–	–	–	3	0.5		
Lateral patella	0	10	83	11	44	363	64	0.13	0.47
	1	2	17	8	32	97	17		
	2	–	–	5	20	79	14		
	3	–	–	1	4	24	4		
Medial patella	0	11	92	20	80	358	64	0.35	**0.003**
	1	–	–	4	16	134	24		
	2	1	8	1	4	58	10		
	3	–	–	–	–	13	2		
Lateral anterior tibia	0	11	92	25	100	562	99.8	0.32	1.0
	1	1	8	–	–	–	–		
	2	–	–	–	–	1	0.2		
Medial anterior tibia	0	10	83	18	72	482	86	0.63	**0.005**
	1	–	–	2	8	51	10		
	2	2	17	3	12	22	3		
	3	–	–	2	8	8	1		
Lateral posterior tibia	0	10	83	24	96	532	94	0.24	0.28
	1	2	17	1	4	24	5		
	2	–	–	–	–	6	1		
	3	–	–	–	–	–	–		
Medial posterior tibia	0	8	67	25	100	523	93	**0.007**	0.35
	1	2	17	–	–	21	4		
	2	1	8	–	–	15	2.3		
	3	1	8	–	–	4	0.7		
Subspinous tibia	0	5	42	4	4	404	72	0.18	**< 0.001**
	1	6	50	14	56	125	22		
	2	–	–	5	20	25	5		
	3	1	8	3	12	8	1		

BML, bone marrow lesion; ACL, anterior cruciate ligament. *P*-values in bold are significant.

predominantly represented on MRI as post-traumatic BMLs, meniscal derangement and cartilage damage in the lateral tibiofemoral compartment.[10,18–20] However, none of the individuals with either a complete or partial rupture of their ACL in our study showed BMLs in the lateral posterior tibial region and instead displayed

predominance toward medial tibiofemoral damage. Interestingly, Frobell *et al.*[19] found that many of these BMLs that were visualized just following knee injury had resolved 2 years after ACL rupture. As the time from ACL injury to MRI acquisition is not known in our study, as well as the fact that the loss of ACL integrity coincides with existing radiographic knee OA, could possibly explain why the previously documented findings of lateral tibiofemoral damage occurring following ACL rupture were not correlated in our study. Frobell also found that age was significantly associated with BML size. The older an individual was at the time of ACL injury was associated with significantly smaller BMLs when compared to adolescents. The average age of our study participants was 61 years, and yet despite not knowing the age of each individual at the time of injury, this may explain why there was no significant difference in large BML location between individuals with a complete or partial ACL tear.

Finally, a reason for the minimal significant differences observed between individuals with a partial or complete ACL tear could be that regardless of how much the ligament is torn, any amount of force applied to the knee that is strong enough to cause even the smallest amount of fiber damage is enough to cause damage to other adjacent knee structures, particularly the subchondral bone underlying the tibial insertion site of the ACL. Thus, any injury to the ACL, no matter how significant, carries a similar prognosis for knee joint health.

When comparing individuals with any ACL tear as seen on MRI to those individuals with an intact ACL, the predominant pattern of joint damage was not significantly different. That is, the majority of joint damage was displayed in the medial tibiofemoral compartment. This suggests that the pattern of osteoarthritic damage found among all these individuals strongly reflects a pattern consistent with an individual having an injured ACL that occurred within the context of OA and that ligament degeneration may have made the ACL ligament more susceptible to trauma. It is unclear whether an incidental ACL tear identified in an individual with established knee OA reflects disease severity and/or contributes further to progression of cartilage loss in the knee.

There are some limitations in our study. First, this is an exploratory study that utilizes a nested case-control within the OAI. Some individuals were selected on the basis of pain and medial joint space width progression. A history of joint injury was established based on participant recall, which introduces an element of recall bias. Further to this the time from reported knee injury to MRI was not recorded in this study. For these reasons it is quite possible that this particular sample will not allow the results of this study to be generalized to a larger community. Further, the number of ACL tears (both partial and complete) is small and this ultimately may be the reason why only minimal significant differences in joint damage between partial and complete ACL injuries were observed. A much larger, more ACL-focused study would need to be performed to better identify relationships between partial and complete tears. Similarly, our sample is much older than a typical ACL injury sample and so any observations made within our study may not be applicable to a younger population.

CONCLUSION

Overall our study showed minimal significant differences in the joint pattern damage between complete and partial tears of the ACL. Knees with prevalent complete ruptures of the ACL did exhibit greater cartilage thinning of the posterior tibia when compared to joints with only a partial ACL tear. Thus any force applied to the knee that is strong enough to cause injury to the ACL carries a similar prognosis for overall knee joint health. All individuals within this study demonstrated a clear predisposition to medial tibiofemoral articular damage regardless of whether they had or did not have an ACL tear as seen on MRI.

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