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The Health and Structural Consequences of Acute Knee Injuries Involving Rupture of the Anterior Cruciate Ligament

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Synopsis

Although there is an abundance of literature regarding the development of knee osteoarthritis following rupture of the anterior cruciate ligament (ACL), the exact mechanism underlying this link is still not clear. Recent studies have reported that a number of factors may be predictive of the subsequent development of osteoarthritis, with damage to the menisci and articular cartilage during the initial trauma, altered knee biomechanics post-injury, and episodic instability chief among them. This article summarizes recent developments in the understanding of the joint damage resulting from an ACL tear, and the influence that current and future treatment methods may have on the long-term progression to osteoarthritis.

Introduction

Despite the recent introduction of biomechanical training initiatives in school and college athletics programs aimed at preventing knee injuries, the knee remains the most commonly injured joint [1]. Although the overall annual rate of injuries stands at 2.29 per 1,000 individuals, the rate of injuries within the 15 to 24 years age-group is almost 70% higher, with organized sporting and recreational activities accounting for the majority of the injuries [1,2].

Of particular interest – in the context of osteoarthritis – are knee injuries resulting in an acute anterior cruciate ligament (ACL) rupture, often accompanied by damage to the chondral articular surface, menisci, subchondral bone and collateral ligaments. Most ACL tears occur in young, active individuals, and require a prolonged lay-off from sport regardless of treatment choice. Standard treatment options include early ligament reconstruction or extensive rehabilitation with the possibility of delayed surgical repair in the event of clinically relevant instability [3]. They are, therefore, potentially expensive injuries, with the cost of surgical reconstruction and rehabilitation estimated to be approximately US$17,000 per patient, in addition to the loss of income related to the short-term functional disability [2,4]. ACL rupture is also strongly linked to the subsequent development of osteoarthritis, with a substantial percentage of patients displaying osteoarthritic changes and related functional disability as early as 10-15 years after the initial injury [5,6]. The possibility of early interventions targeting the structural changes that take place within the knee after ACL rupture may therefore have significant economic and long-term health implications.

This narrative review aims to outline the pattern of joint damage that accompanies an ACL rupture, and the long-term structural changes that predispose the injured knee to the development of osteoarthritis. The current evidence for the efficacy and cost-effectiveness of surgical and non-surgical treatment strategies will also be reviewed.

Mechanisms of ACL injury

ACL rupture is thought to be a result of 'postural readjustments' that simultaneously produce a valgus force and internal or external rotation [3]. This dynamic loading in multiple planes of motion can produce sufficient tension to rupture the ACL [7]. The archetypal scenario in sport is one in which the participant attempts to change direction at the time of landing on the foot, and hence generates a rotational force in addition to the considerable load resulting from decelerating upon landing [8,9].

Most tears therefore occur in sports that involve rapid changes of direction or sudden deceleration [10]. Interestingly, heavy-contact sports like American football and rugby do not demonstrate particularly high injury rates (approximately 0.08 per 1,000 exposures), as most injuries occur in the absence of direct contact [11]. In fact, less contact-based sports like basketball (0.29 per 1,000 exposures for females and 0.08 for males), soccer (0.32 for females and 0.12 for males) and skiing (0.40) have markedly higher injury rates [12-14]. Basketball and soccer account for the largest number of injuries in the US due simply to their superior participation rates [10,15].

The elevated female-male injury ratio has been a consistent finding across numerous studies and sports, and is a particularly well-studied phenomenon [3,10]. Despite this, the exact reason for the higher incidence of ACL tears in women has yet to be elucidated, though it is likely that a number of factors contribute to the finding – most notably differences in quadriceps activation, muscle stiffness, movement patterns during landing and hormone-dependent knee laxity [3,16,17].

Associated injuries

Knee injuries resulting in ACL tears are often associated with a range of additional structural joint damage. Post-traumatic bone lesions (with or without associated osteochondral injury), meniscal damage and collateral ligament injuries are particularly common, and have all been linked with long-term

damage to the synovial joint [18-21]. These associated injuries are therefore worth discussing due to their potential role in the development of osteoarthritic changes.

Post-traumatic bone marrow lesions

Post-traumatic bone marrow lesions (BMLs, also called 'bone bruises' or 'contusions') are observed on magnetic resonance (MR) imaging as regions of diffuse signal abnormality in the subchondral bone marrow [22]. These contusions are a result of the impaction forces between the anterolateral femur and the posterolateral tibia that occur during the initial trauma ('kissing lesions'), and are present in virtually all knees with complete ACL rupture [18,23]. The majority of these BMLs occur in the lateral compartment, most notably on the lateral femoral condyle and the posterior lateral tibial plateau due to the valgus distribution of force usually experienced during the injury [18,24] **(Figure 1)**. A recent study by Boks *et al* suggests that, contrary to expectations, reticular post traumatic BMLs are not associated with increased pain severity in posttraumatic knees [25]. Simple post-traumatic BMLs without involvement of the articular surface are thus likely to be benign occurrences [26,27]. As such, post-traumatic BMLs generally resolve without sequelae within 6-12 months following the injury, though new BMLs have been shown to develop in approximately one-third of ACL-injured knees over the first two years post-injury [26-28].

In contrast, BMLs that are accompanied by disruption to the articular surface are predictive of long term osteochondral sequelae [29-31]. Johnson *et al* found significant proteoglycan loss, chondrocyte injury and matrix degeneration in the articular cartilage adjacent to a geographic BML, as well as osteocyte necrosis within the affected bone marrow [32]. A separate follow-up study by Theologis *et al* found that the matrix composition in cartilage overlying bruises in the lateral tibia was still abnormal one year post-injury despite most of the original osteochondral lesions healing almost completely within 2 weeks to 6 months [18]. This indicates that the initial cartilage injury accompanying geographic bone bruises, osteochondral defects and cortical impactions may lead to sustained cartilage trauma, and could therefore play a role in long-term osteoarthritic changes [22].

Large BML volumes have also been shown to be associated with the presence of cortical depression fractures, which are likely to be of greater short-term clinical relevance than the presence of a simple BML [23,33]. A recent study published by Kijowski *et al* reported that patients with cortical

depression fractures had lower IKDC clinical outcome scores one year after injury, and higher rates of meniscal tears [33].

Meniscal injury

Damage to the menisci is observed in approximately 65-75% of ACL-ruptured knees during arthroscopy [19,34]. Traumatic longitudinal tears in the posterior and middle one-third of the medial menisci account for the majority of lesions, although damage to the posterior-middle portion of the lateral meniscus is also relatively common [20] **(Figure 2)**. It is still unclear whether this meniscal damage occurs primarily as a result of trauma during the initial injury, or is secondary to the initial trauma and occurs between ACL-rupture and arthroscopy. Retrospective observational studies have suggested that increased time between ACL injury and ligament reconstruction may result in higher rates of meniscal tears, but the fact that the majority of these reports are confounded by indication makes it difficult to interpret their findings [35-39].

Numerous studies have shown that meniscal damage in ACL-insufficient knees is associated with cartilage damage. Murrel *et al* found patients with meniscal injury had a three-fold increased in cartilage damage two years post-injury, and partial or complete menisectomies have long been linked to cartilage damage and earlier-onset osteoarthritic changes [34,40,41]. This may indicate that the role of the menisci in reducing contact stresses and friction within the joint is protective of articular cartilage, and therefore the development of osteoarthritis. It is as yet unclear, however, whether the loss of the meniscal function actually causes articular cartilage damage, or is merely a concurrent destructive occurrence [34].

Direct articular cartilage damage

Nearly half of knee injuries that result in an ACL rupture also cause direct articular cartilage damage, particularly on the medial (41-43%) and lateral (20%) femoral condyles [20,42] **(Figure 3)**. Direct cartilage damage is associated with short-term matrix disruption, chondrocyte necrosis and proteoglycan loss [32]. Though it is not yet known whether these changes are ultimately reversible, or become irreversible if a certain amount of damage is sustained, it is possible that the initial trauma plays a role in instigating the well-described progressive cartilage loss that is characteristic of osteoarthritis [18,32].

A recent study by Frobell *et al* using data from the longtitudinal KANON trial reported that two years post-injury significant cartilage thickening was observed in the central medial aspect of the femur,

whilst marked thinning had occurred in the femoral trochlea and the posterior aspects of both the medial and lateral aspects of the femur [28]. These findings were particularly interesting in the context of osteoarthritis, given that osteoarthritis occurs predominantly in the medial compartment, and that animal models have demonstrated that cartilage hypertrophy precedes the characteristic cartilage breakdown [43].

ACL injury and osteoarthritis

How strong is the link?

As noted by Oiestad *et al* in the 2008 systematic review, the majority of studies assessing the long-term link between ACL rupture and osteoarthritis made use of inconsistent radiologic classification methods and heterogeneous populations with respect to treatment, previous activity levels and the presence of concurrent injuries [44]. It is therefore difficult to draw firm figures from the literature on the prevalence of osteoarthritis following ACL injuries, with reported rates ranging from 10% to 90% at 10 to 15 years post-injury [5].

In their 2009 review, Oiestad *et al* suggested that the lack of a consistent radiologic classification system (7 distinct classification systems were identified in the papers included in the analysis) has resulted in the prevalence of knee osteoarthritis following isolated ACL ruptures being greatly overestimated **(Figure 4)**. Oiestad conducted a methodological quality assessment of 31 studies and found that the highest-rated studies reported a prevalence for knee osteoarthritis of 0-13% after isolated rupture of the ACL; significantly lower than the 50-70% prevalence rate often quoted in the literature [45-47]. Combined injuries involving ACL rupture and meniscal damage, however, resulted in a higher prevalence of osteoarthritis of 21-48%. As previously discussed, both meniscal injury and direct articular cartilage trauma are linked to long-term cartilage damage following a knee injury and are predictive of long term tibiofemoral and patellofemoral osteoarthritis [48]. Given that isolated rupture of the ACL is relatively rare, and the majority of ACL ruptures are accompanied by meniscal and chondral damage, the overall rate of osteoarthritis following an injury resulting in an ACL rupture is likely to be closer to the quoted 'combined injury' rate than that reported for 'isolated injuries' [19,20,34].

Why the increased prevalence of OA following ACL rupture?

It has long been suggested that osteochondral damage and intra-articular bleeding experienced during the initial trauma may induce a cascade of biochemical events within the joint that result in the development of osteoarthritis [49]. Recent studies appear to support this idea, with Sward *et al* reporting that an acute knee injury is associated with an immediate local biochemical response; potentially affecting the adjacent cartilage and bone in addition to inducing inflammation [50]. Currently, however, little is known about the relationship between the immediate release of traumatic factors and subsequent osteoarthritis development, though the area is gaining increasing interest.

Recurrent episodes of instability may also play a role in initiating the pathologic changes to the articular cartilage observed post-injury. It has previously been postulated that frequent episodes of instability or pivot-shifting could result in sustained damage to both the articular cartilage and menisci that eventually results in loss of the cartilage[51]. The extent to which cartilage must be damaged in the initial trauma before structural damage becomes irreversible is not yet known, but it is possible that the regular occurrence of instability-related trauma and altered biomechanical loading could overwhelm the limited restorative capacity of the joint and lead to longer-term osteoarthritic changes [32]. Concurrent injury to the menisci and the corresponding loss of its protective function would merely serve to exacerbate the damage to articular cartilage [34].

Although reconstructive surgery can partially restore joint stability following ACL rupture, it is unlikely that surgery fully restores normal biomechanical loading across the knee [45,52-54]. An altered loading pattern causes a shift in compressive and tension load-bearing to unconditioned regions, and reduces loads in conditioned regions [55,56]. Numerous studies have described adaptations by cartilage to altered loading: chondrocyte metabolism and volume:aspect ratio, proteoglycan production, collagen fibre orientation and matrix metalloproteinase expression are all altered during the cartilage response [57,58]. It has therefore been suggested that early changes in cartilage may be partially explained by the altered biomechanics of the knee post-injury [55].

Surgical vs. non-surgical treatment

Despite a paucity of evidence that ACL reconstruction is the most effective treatment for an ACL rupture, over 200,000 procedures are performed each year in the United States alone [59-61]. Allografts, ipsilateral bone-patellar tendon-bone (BPTB) autografts and quadruple hamstring tendon (HT) autografts are currently the most commonly used procedures [62,63]. Recent meta-analyses have suggested that although the three procedures produce similar long-term functional outcomes, allografts and HT autografts may be associated with lower rates of anterior knee pain [63-66].

The short-term benefits of surgical intervention in relation to non-surgical treatments are still unclear, and a number of recent studies have reported that surgery and rehabilitation-alone may produce comparable functionality [61]. Frobell *et al* (2010) conducted a randomized trial in which patients were assigned to receive either structured rehabilitation and early reconstruction or structured rehabilitation alone (with the option of delayed ACL reconstruction) [61]. They reported that although early surgical treatment was associated with greater measured stability in Lachman and pivot-shift tests, after two years there were no significant differences between the treatment groups with respect to patient-relevant outcomes, knee-related adverse events or return to pre-injury activity levels. Similarly, a prospective cohort study by Moknes *et al* found no difference in performance-based outcomes and the number of subjects returning to pre-injury activity levels between non-operatively and operatively treated groups [67]. In a case-control study Meuffels *et al* also found no statistical difference in activity levels or subjective and objective functional outcomes at 10 years post-injury between patients treated conservatively or operatively [68].

ACL reconstructions are commonly advocated on the basis that they are protective against secondary meniscal injury, and thereby reduce the risk of osteoarthritis development. Numerous retrospective studies have suggested that an increased time between injury and reconstruction is associated with higher rates of chondral and meniscal injuries [69,70]. The studies are largely confounded by indication, however, as the fact that patients have symptomatic meniscal or cartilage injuries means they are simply more likely to undergo surgery. A long-term follow up of a previous randomized controlled trial showed that although the rate of secondary meniscal surgery was indeed higher following non-surgical treatment, there was no statistical difference in terms of radiographic osteoarthritis [45]. A 2007 systematic review had similar findings, reporting that no treatment-related differences in osteoarthritis could be found within the literature [5].

It is similarly unclear whether ACL reconstruction decreases the incidence of osteoarthritis development over the long-term. That osteoarthritis still develops in a substantial portion of patients treated with surgical repair is beyond doubt, but virtually no high-quality randomized studies comparing non-operative treatment and reconstructive surgery have been conducted [5,6,71]. A case-control study by Meuffels *et al* found no statistical difference in radiographic osteoarthritis prevalence between the operatively and non-surgically treated groups. In 2007 Meunier *et al* published the results of a 15 year-long trial in which two groups were allocated to receive either surgical treatment or conservative non-surgical treatment on the basis of their year of birth (*odd or even*), and no statistically significant differences in osteoarthritis development were identified between the two groups [45]. The authors did, however, note that there were several major problems with the randomization procedures used when the study was initiated in the early 1980's, most notably the exclusion of some patients from the surgical group because their injuries were not deemed to be 'amenable' to surgical treatment, and the markedly different rehabilitation protocols used across the groups. This is symptomatic of the difficulties faced in attempting a meta-analysis, with the available studies all being of poor methodological quality or of insufficient length to allow a proper evaluation of osteoarthritis development [5,64]. As noted in a recent Cochrane review, there is therefore a need for long-term randomized trials comparing surgical reconstruction and non-surgical treatment in order to establish the efficacy of surgical repair in reducing the incidence of osteoarthritis [72].

On the basis of the limited evidence available, however, there is little to suggest that surgical intervention is significantly superior to conservative rehabilitation in terms of decreasing the rate of osteoarthritis. [5,61]

Economics of ACL rupture

Given the initially debilitating nature of the injury, an ACL tear necessarily produces an array of indirect costs: personal loss of income due to time away from work; government-funded injury leave (in certain countries); absence from school or university; and the loss of conditioning resulting from reduced activity [3]. It is, of course, difficult to adequately measure these indirect costs, but they must be considered when devising an appropriate patient-oriented treatment strategy [73]. An athlete's desire to return to sport within the shortest possible time-frame, in order to avoid deconditioning and subsequent

disruption to their sporting career, may increase a physician's willingness to recommend surgical reconstruction. Currently, one of the primary indications for reconstructive surgery is the need for the subject to quickly resume sporting activities [74,75], though a recent-meta analysis of 5770 individuals who underwent reconstruction found that only 44% had actually returned to competitive sport at a mean follow-up of 41.5 months post-injury [76]. This must also be balanced against the risk of re-injury that accompanies an early return to sport. The asymmetrical limb loading observed in patients up to 15 months post-surgery has been shown to significantly increase the risk of a new ipsi-lateral or contra-lateral ACL injury suggesting that a longer period of rehabilitation than typically advocated may be required for a successful long-term return to sport [75,77-79]. A conservative, non-surgical rehabilitation plan may suffice for a patient for whom the indirect cost of an extended layoff from sport is lower, as it is likely that their long term functional outcome will not differ greatly from that of the surgically-reconstructed patient, and the direct costs of treatment will be significantly less [61,67]. The indirect costs incurred by the patient as a result of the injury or particular treatment protocol are therefore worthy of consideration.

The direct costs associated with ACL rupture are considerable, with the cost of reconstructions alone estimated to be $3 billion USD annually in the United States [80]. On an individual level, expected health care costs with operative treatment lie somewhere between $US11,000-17,000 , with the main contributors being the surgery itself and the subsequent in-hospital stay [2,4,81,82]. Modeling studies by Gottlob *et al* and Farshad *et al* calculated that the cost of non-operative treatment – largely due to physician services and structured rehabilitation – would be closer to $US2,000-2,500 [81,83]. It is interesting to note that although both studies found ACL reconstruction to be slightly more cost-effective than conservative treatment due to the lower cost per quality-adjusted life year (20,612 USD vs. 23,391USD), the authors acknowledged that this was largely based on the assumption that surgical repair significantly reduces the rate of sequelae such as osteoarthritis – an assumption that currently lacks any firm evidence. The general assumption that ACL reconstruction is a cost-effective procedure could therefore be questioned, and further randomized controlled trials need to be conducted in order to properly assess the cost-effectiveness of both surgical and conservative treatment protocols.

Future treatments

Prevention

Given the high risk of knee osteoarthritis following ACL rupture, and the apparent inefficacy of current treatment regimens in reducing rates of osteoarthritis, prevention of the injury must be afforded a high priority. A number of studies have attempted to assess the effectiveness of prevention programs in reducing the incidence of ACL ruptures, with most reporting a moderately successful outcome [84-88]. The actual forms of intervention have varied widely, with neuromuscular training, strengthening activities, aerobic conditioning, plyometrics, resistance training, speed training and education among the more common methods employed within the program [3,89]. A recent systematic review by Gagnier *et al* of eight cohort studies and six randomized trials found a reduction in the rate of ACL ruptures by approximately 50% in the training groups across the 14 studies [89]. Meta-analyses conducted by Hewett *et al* and Grindstaff *et al* reported similar results, with fixed-effect estimates of 0.40 and 0.30, respectively [90,91]. The heterogeneity and complexity of the training programs meant that it was not possible to determine which particular components of the programs were effective, so future studies comparing isolated training techniques are required [89]. Despite this, the fact that training programs have demonstrated the capacity to reduce ACL tear rates is encouraging. Although such programs are currently expensive, the prevention of a substantial portion of annual ACL tears would undoubtedly bring about considerable savings in terms of treatment costs and long-term osteoarthritis-related disability [92].

Early intervention

The possibility that the initial biochemical response to the trauma incurred during ACL rupture may be involved in initiating the series of events that eventually culminates in osteoarthritis implies that prevention or moderation of this acute response may have a significant impact on disease progression [49]. Given that this biochemical response is still but poorly understood, the means to alter it are some time away, but will undoubtedly be of considerable interest in the future.

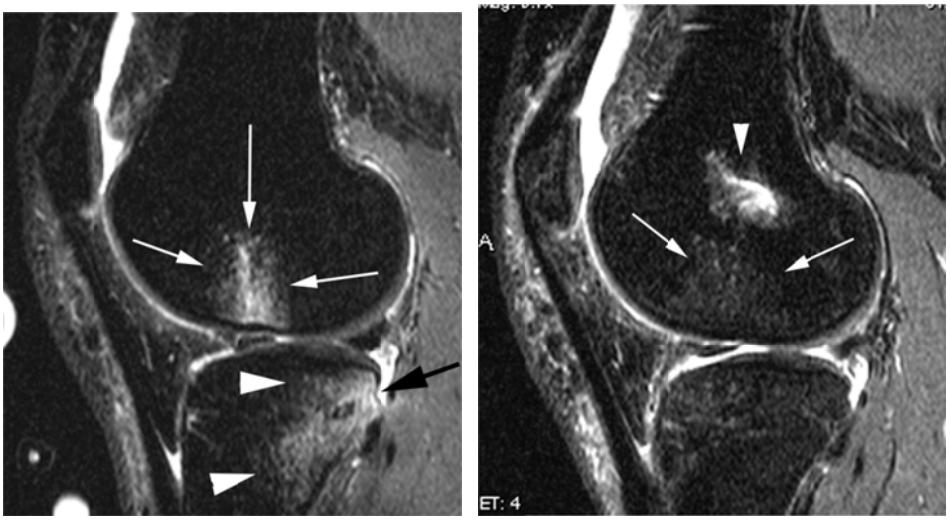
The observations that early changes in the articular cartilage and menisci are associated with the long-term development of osteoarthritis would appear to suggest that an intervention to correct these initial changes would also be protective against future osteoarthritis [41,48]. Meniscal repair and surgical reconstruction do not seem to reduce the risk, however, raising the possibilities that interventions must occur earlier (i.e. irreparable damage has already occurred by the time surgery takes place), or must focus on the articular cartilage and ensuing synovitis itself [5,93]. It would be interesting to investigate whether prevention of the initial cartilage change described in numerous studies would alter the

subsequent pattern of joint damage [28]. Though it is likely that the means to implement any such intervention are still years away, it is probable that halting the early articular changes would have a significant impact on long-term disease progression.

Conclusion

There is considerable evidence to suggest that the associated joint damage incurred during – and immediately after – the initial ACL rupture may be predictive of the subsequent development of osteoarthritis. Although the mechanism of this increased susceptibility is not yet clear, initial trauma to the osteochondral unit, the immediate biochemical response, loss of the protective function of the menisci and biomechanics-related cartilage damage are likely to be significant factors. Reconstructive surgery has not yet been shown to reduce the rate of osteoarthritis development, and it is probable that a successful preventative treatment must be delivered rapidly post-injury to address the early pattern of joint damage changes. The most effective current treatment for ACL injuries, therefore, appears to be prevention of the initial ACL rupture, with several large studies demonstrating success in reducing ACL tear rates.

Figures and Figure Captions



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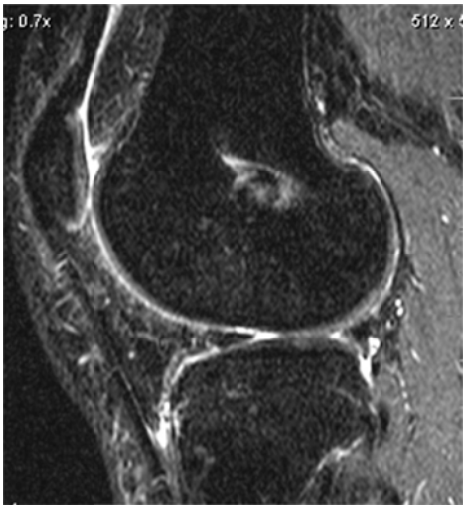


C

Figure 1. Characteristic traumatic bone marrow lesions without associated osteochondral injury after rotational trauma. A 28 year old patient suffered complete ACL disruption. A. The most common locations of traumatic bone changes in conjunction with ACL disruption are the central lateral femoral condyle (white arrows) and the posterior lateral tibial plateau (arrowheads). Bone contusions are characterized by signal hyperintensity on fat suppressed water sensitive sequences. In addition there is a subchondral fracture of the posterior lateral tibial plateau (black arrow). B. At 4 months follow up there is almost complete resolution of bone marrow lesions. Only minimal residual hyperintensity is still observed in the central lateral femur. Note susceptibility artifact due to femoral metallic screw after ACL reconstruction that may be mistaken as a post-traumatic bone marrow edema-like lesion (arrowhead). C. At 12 months follow-up there is complete resolution of subchondral bone changes. Cortical depression of lateral tibial plateau is persistently observed.

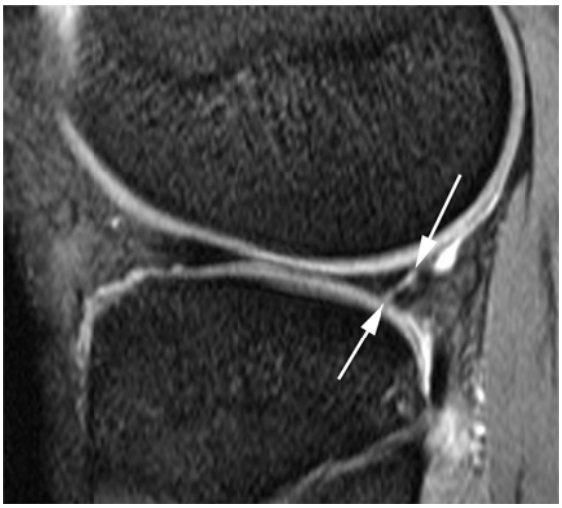
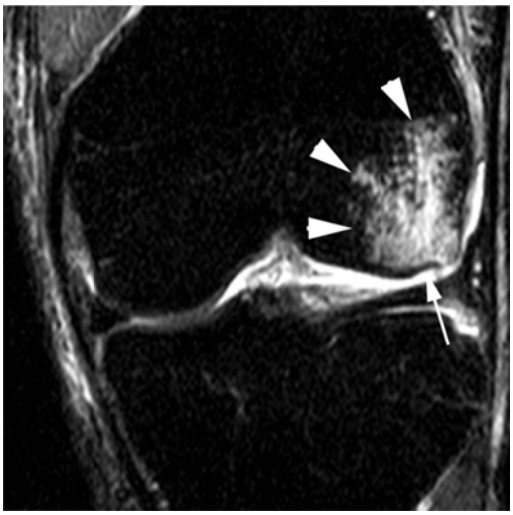


Figure 2. Sagittal dual echo at steady stae (DESS) image shows a longitudinal meniscal tear of the posterior horn of the lateral meniscus in conjunction with a complete ACL disruption. Tear is characterized by a longitudinal hyperintense line extending from the meniscal upper-surface to the under-surface (arrows).



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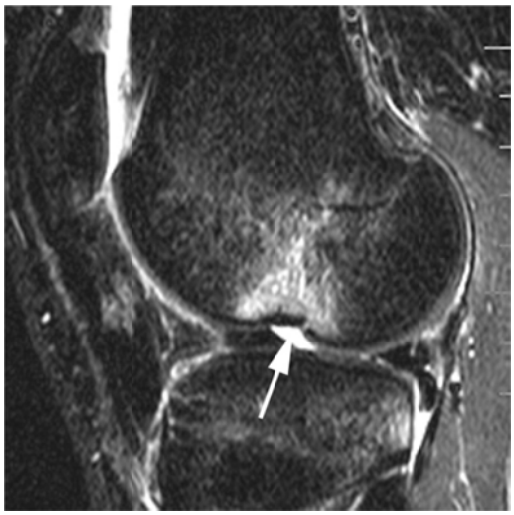

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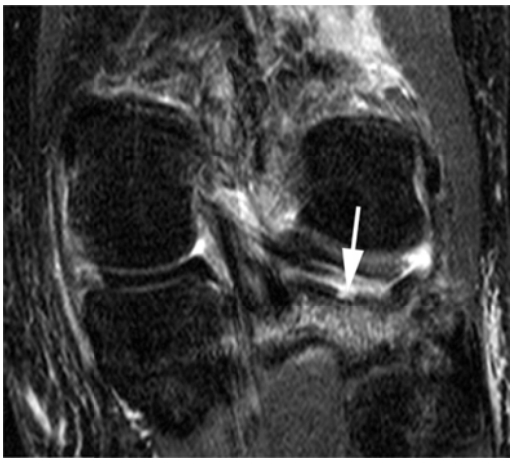

C

Figure 3. Traumatic articular cartilage damage in conjunction with ACL disruption. A. Coronal T2 weighted fat suppressed image exhibits a traumatic bone marrow lesion in the lateral femoral condyle (arrowheads) and an osteochondral depression (arrow). B. Corresponding sagittal image shows depression and disruption of the articular surface (arrow). C. Coronal STIR image of different patient shows an example of a traumatic focal cartilage defect in the posterior lateral tibial plateau (arrow). Note subchondral traumatic bone marrow lesion adjacent to defect reflected as hyperintensity in the subchondral bone marrow.

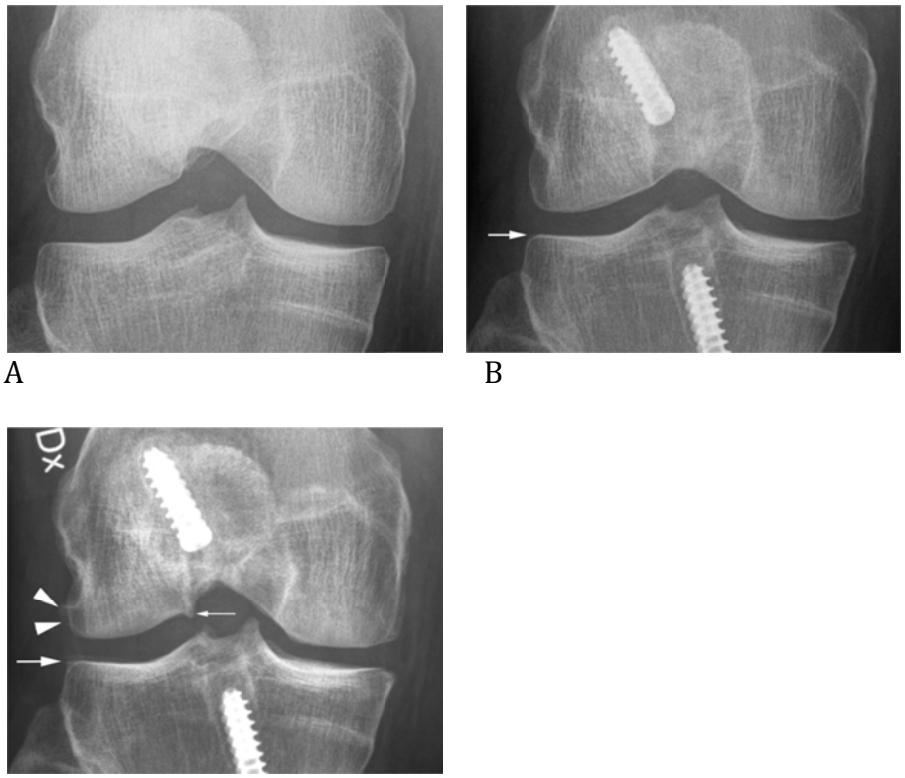

Figure 4. Radiographic osteoarthritis development over 5 years. A. AP radiograph at baseline obtained directly after trauma shows no signs of radiographic osteoarthritis. Normal medial and lateral joint space width and absence of osteophytes are observed. B. 2 year follow-up image shows metallic screws in the femur and tibia after ACL reconstruction. Normal joint space width is observed. There is a tiny equivocal marginal osteophyte at the lateral tibial plateau. C. At 5 years follow-up definite osteophytes are observed at the lateral femoral condyle (arrowheads) and tibial plateau (large arrow) representing radiographic osteoarthritis grade 2 according to the Kellgren-Lawrence classification scheme. In addition there is a prominent notch osteophyte at the lateral femoral condyle potentially causing ligament impingement (small arrow).

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