Published in final edited form as:

Curr Opin Orthop. 2005 October ; 16(5): 354–362.

Ligament Injury, Reconstruction and Osteoarthritis

Braden C. Fleming, Michael J. Hulstyn, Heidi L. Oksendahl, and Paul D. Fadale

Brown Medical School, Rhode Island Hospital, Providence, Rhode Island, USA

Abstract

Purpose of Review—The recent literature on the factors that initiate and accelerate the progression of osteoarthritis following ligament injuries and their treatment is reviewed.

Recent Findings—The ligament-injured joint is at high risk for osteoarthritis. Current conservative (e.g. rehabilitation) and surgical (e.g. reconstruction) treatment options appear not to reduce osteoarthritis following ligament injury. The extent of osteoarthritis does not appear dependent on which joint is affected, or the presence of damage to other tissues within the joint. Mechanical instability is the likely initiator of osteoarthritis in the ligament-injured patient.

Summary—The mechanism osteoarthritis begins with the injury rendering the joint unstable. The instability increases the sliding between the joint surfaces and reduces the efficiency of the muscles, factors that alter joint contact mechanics. The load distribution in the cartilage and underlying bone is disrupted, causing wear and increasing shear, which eventually leads to the osteochondral degeneration. The catalyst to the mechanical process is the inflammation response induced by the injury and sustained during healing. In contrast, the inflammation could be responsible for onset, while the mechanical factors accelerate progression. The mechanisms leading to osteoarthritis following ligament injury have not been fully established. A better understanding of these mechanisms should lead to alternative surgical, drug, and tissue-engineering treatment options, which could eliminate osteoarthritis in these patients. Progress is being made on all fronts. Considering that osteoarthritis is likely to occur despite current treatment options, the best solution may be prevention.

Keywords

anterior cruciate ligament; cartilage; ligament; osteoarthritis; reconstruction; rehabilitation

Introduction

Ligament injuries frequently occur in human joints during sports and trauma, and they place a patient at risk to osteoarthritis early after trauma. Ligament injuries can present themselves in several forms: a complete tear, a partial tear, a stretch injury (plastic deformation), or an alteration in function caused by an adjacent fracture. No matter what the type of injury, a distinct sequence of events occurs that initiates the degenerative cycle leading to osteoarthritis.

A traumatic event that dislocates the joint produces the initial ligament injury. The injury may occur in isolation or in combination with other tissues of the joint (i.e. capsule, fibrocartilage, cartilage, and/or subchondral bone). Joint stability is compromised, which in turn alters the motion (kinematics) between the bones when the joint is loaded and changes the articular contact mechanics (the magnitude, direction, and location of contact). The abnormal contact

Correspondence to Braden C. Fleming, PhD, Brown Medical School, CORO West, Suite 404, 1 Hoppin Street, Providence, RI 02903, USA Tel: 401 444 4164; fax: 401 444 4418; e-mail: Braden_Fleming@brown.edu

Sponsorship: Supported by grants from the National Institutes of Health (AR049199 and AR047910).

mechanics along with the inflammation cascade alter the metabolism of the cartilage and underlying bone, disrupt the homeostasis of the joint, cause wear, and increase shear loading. The instability places the other structures of the joint at greater risk to subsequent injury, which exacerbates the problem.

The details underlying the mechanisms behind cartilage degeneration following ligament injury have not been determined. Many confounding biochemical and mechanical factors need to be considered (Fig. 1). If the mechanisms of osteoarthritis progression are established, our ability to intervene and reverse the process may become reality.

Pathomechanics of the ligament-deficient joint

Ligament injuries are very common, and they typically afflict the younger population. The knee is particularly prone to ligament injury because it is located between the two longest lever arms in the body (i.e. the tibia and femur), and it is subjected to high repetitive impact loads. It is estimated that the average person takes approximately 1.2 million steps per year, and resultant forces of up to five times body weight occur with each step. These statistics emphasize the harsh mechanical environment the articular cartilage, subchondral bone, ligaments, menisci, and joint capsule must endure. The ligaments are passive stabilizers of the knee, so they guide motion between the tibia and femur and hence define the articular contact mechanics. They also act as restraints to prevent excessive motion (i.e. dislocations). Thus, a knee ligament injury disrupts the balance of force between the knee structures, altering the tibiofemoral contact location.

Although the relation between ligament injuries and osteoarthritis is usually studied in the knee, it is a problem relevant to all joints, particularly those that are highly dependent on the ligaments for stability (i.e. thumb, wrist, shoulder, ankle, and toe) [1•]. In the carpometacarpal joint, a dislocation injury may occur when a high-impact axial load is applied to the flexed thumb. Excessive load will damage the ligaments and produce pathologic laxity [2]. This abnormal laxity increases the translations between the trapezium and metacarpal, and the shear forces at the cartilage bone interface, which is hypothesized to damage the articular cartilage [2,3•]. In the wrist, a traumatic injury to the radioulnar ligaments, such as that which occurs with impact applied to an outstretched pronated hand, can result in a severe joint instability, placing the joint at risk for osteoarthritis [4]. The term *dislocation arthropathy* was coined by Samilson and Prieto [5•] to describe the relation between shoulder instability and osteoarthritis. In a retrospective follow-up of 570 patients who underwent surgical instability procedures for the shoulder, osteoarthritis was prevalent in 8.4% of the patients preoperatively (mean time to surgery, 4 years), and treatment did not retard progression [5•]. Ligament instability has also been linked to osteoarthritis in the ankle [6•,7]. A recent evaluation determined that 78% of cadavers with damaged anterior talofibular and/or calcaneofibular ligaments had evidence of osteoarthritis, compared with 50% in age-matched and sex-matched controls [6•]. Turf toe is an injury that occurs when the capsuloligamentous structures are damaged as an external force hyperextends the joint. It is implicated in placing the metatarsal phalangeal joint at risk for osteoarthritis [1•]. These examples provide credence to the hypothesis that ligament damage in a synovial joint will lead to the onset and progression of osteoarthritis after trauma.

Anterior cruciate ligament problem

Most of our knowledge regarding ligament injuries and osteoarthritis has been obtained from studying the anterior cruciate ligament (ACL)-deficient knee. Over 80,000 ACL tears occur in the United States each year [8]. The injury produces a severe functional deficit that places the patient at risk for early osteoarthritis [9•,10••-13••,14]. Hill *et al.* [15••] determined that 23% of a cohort of patients being treated for primary osteoarthritis had ACL ruptures (compared with 3% in a matched control group), and they found that the degenerative changes were more

severe in the ACL-injured patients compared with the ACL-intact patients with osteoarthritis. Arthroscopic assessment of the cartilage surface demonstrates that distinct degenerative changes (fibrillation and chondral lesions) occur in the ACL-deficient patient, and these have been shown to relate to lower structural properties of the tissue [9,16•].

A recent retrospective study involving 205 men who ruptured an ACL while playing competitive soccer determined that there was radiographic evidence of osteoarthritis 14 years after injury. Of the patients, 78% had degenerative signs in their injured knee, compared with 4% in their uninjured knee [13•]. Patients with radiographic evidence of osteoarthritis reported symptoms that significantly affected their quality of life. Similar statistics were reported from a cohort of competitive female soccer players 12 years after injury [12•].

Pond-Nuki model

The ACL-transection (ACLT) model is extensively used to study osteoarthritis and its treatment [17•,18,19•,20•,21•-24•,25,26•,27•,28,29,30•,31,32,33•,34,35•,36•,37•,38]. In this model, the ligament is sectioned to initiate osteoarthritis. Biochemical changes to the cartilage have been shown to occur within 3 weeks of the surgical intervention, and long-term progression has been shown to mimic that of humans [38,39,40]. Details regarding the progression of osteoarthritis in the ACLT model continue to be identified as new measurement techniques (i.e. magnetic resonance imaging [MRI], micro-computed tomography, microscopy, biochemical markers, gene expression) are employed [17•,19•,20•,21•,25,26•,28].

Bone marrow edema beneath the medial compartment of the tibial plateau is detected with MRI within 6 weeks of ACLT in the dog. Evidence of cartilage erosion is present by the 12th week, and osteophytosis and subsequent meniscal damage occur by the 24th week [21•]. Alhadlaq *et al.* [37•] determined that there is a 38% decrease in the thickness of the superficial zone of articular cartilage, which coincides with a 15–27% increase in the total cartilage thickness by the 12th week using MRI and microscopy. Using MRI and micro-computed tomography, significant subchondral bone loss is shown to occur within 8 weeks of surgery. It recovers by the 12th week, however, indicating that remodeling is able to compensate for the initial injury [25,26•]. Despite remodeling efforts, subchondral sclerosis becomes evident within 6 months of ACLT [33•].

Articular cartilage continually undergoes metabolic activity to synthesize and degrade its matrix. With metabolic activity, enzymes, matrix fragments, and precursor molecules (biomarkers) are released into synovial fluid, transferred to the blood and lymph, and excreted through the urine. When metabolic homeostasis is lost, imbalances in the concentrations of different biomarkers occur that may provide insight into the pathophysiology of the cartilage. Matyas *et al.* [19•] used the canine ACLT model to evaluate the sensitivity of several biochemical markers of articular cartilage metabolism: proteoglycan aggrecan turnover, type II collagen synthesis, and degradation. The biomarker concentrations were measured preoperatively and after 3 and 12 weeks of healing after ACLT. The biomarker levels were compared against a macroscopic grading scale [19•]. They reported that the biomarkers of aggrecan turnover (the 846-epitope of aggrecan in serum) and type II collagen degradation (C2C and Col2CTx in serum and synovial fluid) were efficacious for the detection of early degenerative changes [19•]. These and other biomarkers of articular cartilage and bone metabolism may provide useful tools to assess cartilage degradation for animal [19•,24•,41] and clinical studies of ligament injury and treatment [42,43•].

Some of the molecular mechanisms underlying the early stages of osteoarthritis have also been established using the ACLT model. Lorenz *et al.* [20•] recently evaluated gene expression levels of matrix molecules and cytokines. They determined that collagen II, collagen I, and

YKL40 (a chitinase-like molecule linked to tissue remodeling/inflammation) were up-regulated within 6 weeks of ACLT and remained elevated throughout the 48-week study period. MMP-13 (a metalloproteinase) and aggrecan synthesis remained unchanged until 24 and 48 weeks after ACLT, respectively. These changes are expected to be similar to those inherent to human osteoarthritis [20••].

The applicability of the ACLT model to study osteoarthritis and potential treatment alternatives provides further support that joint instability is the primary factor for the onset and progression of osteoarthritis following ligament disruption. Many confounding variables are controlled with this model, including the time between injury and treatment, impact trauma to the subchondral bone, and concomitant injuries to associated structures. The use of sham animals, a hallmark of a well designed study, accounts for the surgical inflammation response. It should be noted that degeneration is observed in the contra-lateral knee as well, suggesting a bilateral effect [33•].

Current ligament reconstruction procedures may not eliminate osteoarthritis

Approximately two-thirds of the patients presenting with an ACL tear are surgically reconstructed with a tendon graft. The surgical objectives are to reestablish function and to prevent subsequent damage to the articular cartilage and other soft tissue structures [44]. The ability of autogenous patellar tendon and hamstring tendon grafts to restore function is well accepted [45]. Evidence suggests that cartilage degeneration will progress despite surgery, however [3•,5•,10••-13••,16••,43••].

Many patients who undergo ACL reconstruction exhibit early radiographic evidence of osteoarthritis [11••-13•• 16••,44,46-51]. Johma *et al.* [47] reported that 11% of the patients who underwent acute ACL reconstruction and 50% of the patients who underwent chronic ACL reconstruction presented radiographic evidence of osteoarthritis after 7 years. The evidence suggests that cartilage damage becomes more severe as the time between injury and surgery increases [47,50•]. In a 5-year prospective follow-up, Daniel *et al.* [46] determined that both acute and chronic ACL-reconstructed knees had significantly greater radiographic evidence of osteoarthritis compared with the conservatively treated group. Recently, radiographic evidence of osteoarthritis in the ACL-reconstructed knee was similar to that in knees treated conservatively (78%) and significantly greater than that of the contra-lateral uninjured knee (4%) in competitive soccer players after 14 years of healing [13••]. Asano *et al.* [16••] prospectively evaluated articular cartilage status via second look arthroscopy in 105 patients following ACL reconstruction with a hamstrings tendon autograft. They established that the articular cartilage continued to degenerate in all patients [16••]. This finding contrasts with that of a randomized clinical trial finding that the radiographic evidence of osteoarthritis in only 4% of the patients who received a hamstring tendon graft compared with 18% of the patients who received patellar tendon grafts after 5 years of healing [44].

A recent prospective randomized control trial comparing two protocols for rehabilitation after operation (accelerated compared with nonaccelerated rehabilitation) following ACL reconstruction with patellar tendon graft provides further evidence that articular cartilage metabolism is altered following an isolated ACL injury and reconstruction [43••]. Articular cartilage status was evaluating using bio-markers of cartilage metabolism in synovial fluid [43••]. Patients were included only if they had an isolated acute unilateral ACL injury and no prior history of knee problems. Synovial fluid was aspirated from both knees intraoperatively and after 3, 6, 12, and 24 months of healing. Samples were also obtained from control participants with no knee injuries. No differences in biomarker concentrations for collagen breakdown (C2C epitope), collagen synthesis (C-propeptide of collagen II), and proteoglycan turnover (846-epitope of aggrecan) were found between the rehabilitation programs. The

concentrations of all three biomarkers were elevated before reconstruction, however, and remained elevated for at least 6 months after surgery. The collagen breakdown biomarker returned to normal by the 12th month, while the collagen synthesis biomarker remained elevated through the 24th month. The bio-marker of aggrecan turnover approached that of the normal joint by the 24th month. It is unknown whether the biomarker concentrations will stabilize or continue to drop beyond 24 months (Fig. 2). These data clearly show that articular cartilage metabolism is affected by the injury and surgical treatment for at least 2 years following surgery.

Most studies evaluating the incidence of osteoarthritis following ACL injury and reconstruction are not sufficient to establish cause and effect because they are not based on prospective randomized clinical trials. Several sources of bias must be considered. Some studies are limited to patients who participate only in competitive sport, while others do randomize patients to a particular patient group. For example, patients who are more active will typically select surgical treatment, while sedentary patients tend to select conservative treatment, factors that may have a pronounced effect on the progression of osteoarthritis within each treatment. The effects of the many confounding variables (e.g. meniscal and osteochondral damage) are not generally considered [41,50,52-55]. Detection bias is also a factor because most studies use techniques that are not sensitive to early degenerative changes. Nonetheless, they provide strong evidence that a ligament injury will initiate osteoarthritis, and current treatment options are unable to stop progression.

Potential factors producing osteoarthritis following ligament injury

The primary factor responsible for the onset and progression of the osteoarthritis is joint instability. Ligaments limit joint motion, so the injury will increase sliding between the surfaces, which in turn alters the articular contact mechanics [56•,57•]. Cartilage is thickest where the contact pressure is the greatest [56•,58]. With injury, the envelope of joint motion becomes larger, producing a tibiofemoral offset that may transfer the contact stresses to regions where the thinner cartilage may be less able to support them and increase the shear stress at the cartilage–bone interface [56•]. This in turn may increase the external adduction moment and increase the load in the medial compartment, accelerating progression [15•]. The instability also increases the stresses on the secondary stabilizers of the joint, which can further exacerbate the problem.

An ACL injury alters the kinematics of the knee, placing the ACL-deficient patient at risk for early osteoarthritis [57•]. It seems intuitive that a reconstructive procedure would restore ligament function and hence stop the progression of osteoarthritis if kinematics were restored. Bio-mechanical studies have been performed to determine whether the kinematics of the ACL-reconstructed knee are normal [10•,59•,60•,61•,62•,63,64•]. Although it may be possible to restore stability to the knee in one plane using current reconstruction procedures, this is not the case when considering all planes of motion [10•,59•,60•,61•,62•,63,64•]. This may be a result of the differences in graft structure (compared with the normal ACL), intra-articular graft placement, and initial graft tension. For example, multi-bundle grafts are becoming popular in an effort to replicate the structure of the normal ACL and improve the rotatory kinematics of the knee [59•,65]. In theory, this would reduce the shear forces and hence minimize osteoarthritis progression; however, this effect has yet to be evaluated *in vivo*.

Using planar radiographs, Almekinders *et al.* [10•] reported an 'irreducible tibial subluxation' following ACL reconstruction with patellar tendon autografts. They determined that the neutral tibiofemoral contact area was located more anterior on the tibial plateau even though the overall anterior-posterior laxity of the joint was reestablished [10•]. Using MRI, Logan *et al.* [61•] demonstrated that the tibiofemoral contact conditions were also different following

reconstruction with a hamstring tendon graft. A persistent anterior subluxation of the lateral tibial plateau was noted with weight-bearing when the knee was between 0° and 90° of flexion [61•]. Using stereofluoroscopy, Tashman *et al.* [64•] found that patients with reconstructed knees consistently run with their reconstructed knee externally rotated (by 3.8°) and more adducted (by 2.8°) than the control knee after 12 months of healing. Recently, metabolic activity in the subchondral bone of reconstructed knees was found to be greater than that of control knees 5–9 years after surgery [60•]. Reconstructed knees with a positive pivot shift (an indicator of instability) also had greater scintigraphic activity than those that did not [60•]. These studies verify that normal kinematics are not restored following ACL reconstruction, and that this may be responsible for the onset and progression of osteoarthritis.

Another factor thought to be responsible for the onset and/or progression of osteoarthritis in the ACL-injured patient is the altered joint loading [17•,56•]. Altered joint loading in the ACL-injured or ACL-reconstructed knee may be a result of the joint instability, as described above [56•], or of changes in muscle function as a result of the injury [17•,66–68]. Herzog *et al.* [17•] found that muscle forces are decreased and control patterns disrupted following ACLT in the cat, and that these changes corresponded to a decrease in the structural properties of the cartilage. They speculated that joint unloading and poor muscle control may be a primary factor affecting osteoarthritis in the ACL-deficient patient. Altered muscle function following ACL injury and reconstruction have also been shown to occur in humans [66–68]. Thus, osteoarthritis could be initiated by either too much load in regions not designed to support that load [56•,58] or not enough load to maintain metabolic homeostasis [17•,58].

The ligament injury also induces trauma to the entire joint. Synovitis, effusions, and hematoma are associated with injury and are known to stimulate remodeling in the articular cartilage, the subchondral bone, the injured ligament, and other soft tissue structures in the knee [29,31,53, 69•]. The inflammatory response initiates a cascade of biologic events that includes the release of growth factors and cytokines and stimulates angiogenesis and apoptosis [53]. The initial repair efforts of the ligament will release cytokines that may affect cartilage metabolism [41]. Surgical treatment of a ligament injury could also invigorate the inflammation response.

The prevalence of meniscal tears in an acute ACL injury has been reported in the range of 16–82% [50•]. Conservatively treated ACL-deficient patients are at increased risk for subsequent meniscal damage [11•], which has been shown to place a patient at risk for early cartilage degeneration [46,48,49,50•,55]. Meniscal injuries have been shown by some to increase the risk for osteoarthritis in ACL-reconstructed patients [46,50•,60•], but not by others [11•–13•,16•]. Recently, Fithian *et al.* [11•] found using MRI that the incidence of cartilage degeneration in the ACL-reconstructed patient was 94% and 92% with and without meniscus tears, respectively. In the cohort of competitive soccer players 14 years after injury, Von Porat [13•] reported that 38% of the patients had meniscal tears at the time of injury, though no difference in osteochondral degeneration was noted between the patients with and without meniscal injury. In contrast, Jonsson [60•] found that scintigraphic activity in the subchondral bone was greater in patients with meniscal damage. Considering these studies together, it is possible that the meniscal injury may affect the rate of progression but not the end result.

Damage to the periarticular bone is another potential source of osteoarthritis [50•,70,71,72•, 73,74]. Approximately 80% of the patients receive subchondral bone bruises at the time of ACL injury [50•]. These remain present 2 years following injury or surgical treatment [72•, 74]. The impact loads responsible for the bruise initiate subchondral damage, which accelerates subchondral bone stiffening (i.e. the bone is less able to dissipate energy), osteophytosis, and cyst formation [30•,58]. In a recent study of patients following ACL reconstruction, the presence of a bone bruise did not alter the incidence of cartilage degeneration (91% with contusion compared with 100% without contusion) [11•], suggesting that the effects of a bone

bruise on osteoarthritis progression may not be additive. The patient may be destined for osteoarthritis with the ACL injury alone.

Other treatment options

Neither conservative therapy nor the current surgical reconstruction techniques have been successful in eliminating or slowing the progression of osteoarthritis following ligament injury. Many studies are underway to find adjunct and/or alternative treatments. These include exercise [23•], drug therapies [18,22•,24•,27•,29,30•,31,32,33•,34,35•,75•], visco-supplementation [27•,76], electromagnetic radiation [36•], and tissue engineering [77•,78]. Although these treatments are geared to the treatment of primary osteoarthritis, the ACLT model has been used to evaluate them. Therefore, they provide insight into the treatment of the ligament injuries to prevent osteoarthritis as well.

Galois *et al.* [23•] demonstrated that light to moderate exercise reduced the severity of cartilage lesions via histology using the rat ACLT model. Moderate exercise was shown to up-regulate heat shock proteins that reduce chondrocyte apoptosis. The chondroprotective effect was lost with intense exercise, however. The use of exercise for the treatment and prevention of idiopathic osteoarthritis enhances bone and cartilage metabolism and muscle function, which could slow progression [79].

Although controversial, chondroitin sulfate and glucosamine are dietary supplements frequently taken to reduce cartilage damage. Early clinical evidence suggests that these supplements may reduce joint space narrowing in patients with mild idiopathic osteoarthritis [80]; however, a recent clinical study found no differences in biomarkers of collagen degradation in patients with osteoarthritis taking glucosamine or placebo after 24 weeks of oral treatment [81]. Using the ACLT model in rabbits, investigators have shown that glucosamine had a chondro-protective effect that slowed osteoarthritis progression when injected intra-articularly (visco-supplementation) [27•,82•]. Clinical trials evaluating the effects of glucosamine and chondroitin sulfate for the ligament-injured patient have not been performed. Other drugs targeting inflammation and cartilage repair, including carboxy-methylated chitin and dehydroepiandrosterone, have been shown to slow but not eliminate progression using the ACLT model [29,31].

Drugs effecting bone metabolism have also been evaluated. Biphosphonates reduce bone resorption and provide chondroprotective effects that slow disease progression [30•,75•]. Oral administration of the antibiotic doxycycline has also been thought to limit the progression of osteoarthritis [18]. In the canine ACLT model, subchondral bone remodeling was shown to occur with doxycycline after 36 weeks, but the benefits were not significant by 72 weeks. Thus, therapeutic use of doxycycline has little effect on the mechanics and morphometry of the underlying bone [18]. The effects of calcitonin on slowing cartilage and subchondral bone degradation have been evaluated using the canine ACLT model [22•,24•]. Animals receiving calcitonin maintained better subchondral bone quality and reduced the severity of cartilage lesions.

Exposure to electromagnetic fields has also been shown to stimulate healing in bone and cartilage. Rogachefsky *et al.* [36•] used the canine ACLT model and found that the severity of osteoarthritis in the canine ACLT model was reduced both macroscopically and histologically when the animals were subjected to a magnetic field. MMP-1 and MMP-3 activity were reduced in the treated animals compared with the ACLT animals that were not exposed to the field [36•]. Like most drug treatments to date, it slowed but did not stop osteoarthritis progression.

Conclusion

Ligament injuries place a patient at risk for early osteoarthritis. The mechanisms of cartilage degeneration remain elusive and are most likely multifactorial: mechanical factors (e.g. kinematics, altered joint loading), biologic factors (e.g. inflammation, remodeling), and the presence of associated injuries (subchondral bone bruising, meniscal damage). The ligament injury induces an immediate mechanical instability, so the likely source of degradation is of mechanical origin, while the inflammation response is the likely catalyst (as demonstrated by the ACLT animal model compared with sham animals). The role of the associated injuries remains controversial because some clinical studies have shown that damage to the menisci and subchondral bone may not worsen the long-term condition in the ACL-deficient knee. If we accept that mechanical instability initiates progression, the paradigm recently described by Andriacchi *et al.* [56••] provides a plausible mechanism (Fig. 3). The vicious cycle, once initiated, leads to osteoarthritis.

It is also clear that the current treatment options for the ligament-injured patient may not eliminate osteoarthritis progression. The influence that meniscal and subchondral bone damage may have on osteoarthritis progression in these patients may become clear as better techniques are developed to detect early osteochondral degeneration. Surgical improvements are being pursued in an effort to optimize important surgical parameters (i.e. graft structure, placement, and tension). Tissue engineers are likely to provide innovative biologic grafting materials to replace damaged cartilage and ligaments in the near future [77•], while the molecular biologists are developing methods to stimulate the healing response of damaged ligaments [83]. Prevention of ligament injuries would provide the best solution. If high-risk patients were identified and prevention strategies employed to reduce the injury rate, the osteoarthritis problem caused by ligament injury could be much lower [84].

Abbreviations

ACL, anterior cruciate ligament; ACLT, anterior cruciate ligament-transection; MRI, magnetic resonance imaging.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

- 1•. Koh J, Dietz J. Osteoarthritis in other joints (hip, elbow, foot, toes, wrist) after sports injuries. *Clin Sports Med* 2005;24:57–70. [PubMed: 15636777] A relationship exists between ligament injury and osteoarthritis in the less constrained joints of the body (review article).
2. Connell DA, Pike J, Koulouris G, et al. MR imaging of thumb carpometacarpal joint ligament injuries. *J Hand Surg [Br]* 2004;29:46–54.
- 3•. Martou G, Veltri K, Thoma A. Surgical treatment of osteoarthritis of the carpometacarpal joint of the thumb: a systematic review. *Plast Reconstr Surg* 2004;114:1–32. [PubMed: 15220558]
Ligamentous reconstruction in the CMC joint did not provide a better outcome than arthrodesis or trapeziectomy for the treatment of osteoarthritis (systematic review).
4. Teoh LC, Yam AK. Anatomic reconstruction of the distal radioulnar ligaments: long-term results. *J Hand Surg [Br]* 2005;30:185–193.
- 5•. Samilson RL, Prieto V. Dislocation arthroplasty of the shoulder. *J Bone Joint Surg Am* 1983;65:456–460. [PubMed: 6833319] Osteoarthritis is evident in 9% of patients with shoulder instability, and surgical treatment did not stop progression (retrospective study).

- 6•. Hirose K, Murakami G, Minowa T, et al. Lateral ligament injury of the ankle and associated articular cartilage degeneration in the talocrural joint: anatomic study using elderly cadavers. *J Orthop Sci* 2004;9:37–43. [PubMed: 14767703] The incidence of osteoarthritis with documented ankle ligament damage was greater than that of age-matched and sex-matched controls (cadaver study).
7. Schmidt R, Cordier E, Bertsch C, et al. Reconstruction of the lateral ligaments: do the anatomical procedures restore physiologic ankle kinematics? *Foot Ankle Int* 2004;25:31–36. [PubMed: 14768962]
8. Griffin LY, Agel J, Albohm MJ, et al. Noncontact anterior cruciate ligament injuries: risk factors and prevention strategies. *J Am Acad Orthop Surg* 2000;8:141–150. [PubMed: 10874221]
- 9•. Vasara AI, Jurvelin JS, Peterson L, Kiviranta I. Arthroscopic cartilage indentation and cartilage lesions of anterior cruciate ligament-deficient knees. *Am J Sports Med* 2005;33:408–414. [PubMed: 15716257] The number of lesions seen arthroscopically following ACL injury increase with time from injury. The cartilage located near a lesion was softer than that which appeared normal (cross-sectional observation).
- 10••. Almekinders LC, Pandarinath R, Rahusen FT. Knee stability following anterior cruciate ligament rupture and surgery. The contribution of irreducible tibial subluxation. *J Bone Joint Surg Am* 2004;86:983–987. [PubMed: 15118041] The joint contact mechanics are not restored following ACL reconstruction surgery. The tibia was found to be anterior relative to the femur (retrospective cohort study).
- 11••. Fithian DC, Paxton EW, Stone ML, et al. Prospective trial of a treatment algorithm for the management of the anterior cruciate ligament-injured knee. *Am J Sports Med* 2005;33:335–346. [PubMed: 15716249] Prospective clinical trial (not randomized) finding that the incidence of osteoarthritis in patients treated with reconstruction was similar to that seen in less active patients treated with rehabilitation (prospective controlled trial).
- 12••. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum* 2004;50:3145–3152. [PubMed: 15476248] The incidence of osteoarthritis in female competitive athletes was 82% 12 years after injury. No difference was found in osteoarthritis between patients who were treated conservatively or surgically (retrospective observational study).
- 13••. Von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis* 2004;63:269–273. [PubMed: 14962961] A retrospective comparison reporting that the incidence of osteoarthritis in competitive female athletes was 78% 14 years following injury. It was not affected by surgical or conservative treatment (retrospective observational study).
14. Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. *Osteoarthritis Cartilage* 1995;3:261–267. [PubMed: 8689461]
- 15••. Hill CL, Seo GS, Gale D, et al. Cruciate ligament integrity in osteoarthritis of the knee. *Arthritis Rheum* 2005;52:794–799. [PubMed: 15751064] In a large cohort of patients with osteoarthritis, 22.7% of them had ACL tears, and the degenerative changes were greater than in the patients without an ACL tear (cross-sectional controlled study).
- 16••. Asano H, Muneta T, Ikeda H, et al. Arthroscopic evaluation of the articular cartilage after anterior cruciate ligament reconstruction: a short-term prospective study of 105 patients. *Arthroscopy* 2004;20:474–481. [PubMed: 15122137] One hundred percent of patients undergoing ACL reconstruction with a hamstring tendon graft had signs of early osteoarthritis via second look arthroscopy (cross-sectional case series).
- 17••. Herzog W, Clark A, Longino D. Joint mechanics in osteoarthritis. *Novartis Found Symp* 2004;260:79–95. [PubMed: 15283445] Poses the hypothesis that diminished joint loading in response to diminished muscle function may be the driving factor inducing degeneration in the ACL-deficient knee.
18. Pardy CK, Matyas JR, Zernicke RF. Doxycycline effects on mechanical and morphometrical properties of early- and late-stage osteoarthritic bone following anterior cruciate ligament injury. *J Appl Physiol* 2004;97:1254–1260. [PubMed: 15358750]

- 19••. Matyas JR, Atley L, Ionescu M, et al. Analysis of cartilage biomarkers in the early phases of canine experimental osteoarthritis. *Arthritis Rheum* 2004;50:543–552. [PubMed: 14872497] Biochemical markers of collagen and aggrecan metabolism corresponded well to macroscopic changes.
- 20••. Lorenz H, Wenz W, Ivancic M, et al. Early and stable upregulation of collagen type II, collagen type I and YKL40 expression levels in cartilage during early experimental osteoarthritis occurs independent of joint location and histological grading. *Arthritis Res Ther* 2005;7:R156–R165. [PubMed: 15642136] The ACLT model was used to study the regulation of genes thought to initiate arthritis. Collagen I, II, and YKL40 were up-regulated in the early stages.
- 21•. Libicher M, Ivancic M, Hoffmann V, Wenz W. Early changes in experimental osteoarthritis using the Pond-Nuki dog model: technical procedure and initial results of in vivo MR imaging. *Eur Radiol* 2004;15:390–394. [PubMed: 15365755] Using the ACLT model and MRI, early degenerative changes were detected via MRI, the first of which was bone marrow edema.
- 22•. Behets C, Williams JM, Chappard D, et al. Effects of calcitonin on subchondral trabecular bone changes and on osteoarthritic cartilage lesions after acute anterior cruciate ligament deficiency. *J Bone Miner Res* 2004;19:1821–1826. [PubMed: 15476582] Calcitonin reduced subchondral bone loss and slowed osteoarthritis progression in the canine ACLT model.
- 23•. Galois L, Etienne S, Grossin L, et al. Dose-response relationship for exercise on severity of experimental osteoarthritis in rats: a pilot study. *Osteoarthritis Cartilage* 2004;12:779–786. [PubMed: 15450527] Slight to moderate exercise but not strenuous exercise slowed the progression of osteoarthritis in the ACLT model.
- 24•. El Hajjaji H, Williams JM, Devogelaer JP, et al. Treatment with calcitonin prevents the net loss of collagen, hyaluronan and proteoglycan aggregates from cartilage in the early stages of canine experimental osteoarthritis. *Osteoarthritis Cartilage* 2004;12:904–911. [PubMed: 15501406] Calcitonin reduced the progression of osteoarthritis in the ACLT model and therefore may provide relief in the ACL-injured patient.
25. Batiste DL, Kirkley A, Laverty S, et al. High-resolution MRI and micro-CT in an ex vivo rabbit anterior cruciate ligament transection model of osteoarthritis. *Osteoarthritis Cartilage* 2004;12:614–626. [PubMed: 15262241]
- 26•. Batiste DL, Kirkley A, Laverty S, et al. Ex vivo characterization of articular cartilage and bone lesions in a rabbit ACL transection model of osteoarthritis using MRI and micro-CT. *Osteoarthritis Cartilage* 2004;12:986–996. [PubMed: 15564066] The rabbit ACLT model exhibits progressive cartilage degeneration and subchondral bone changes within 4 weeks of surgery.
- 27•. Shikhman AR, Amiel D, D'Lima D, et al. Chondroprotective activity of N acetylglucosamine in rabbits with experimental osteoarthritis. *Ann Rheum Dis* 2005;64:89–94. [PubMed: 15608304] Intra-articular injections of glucosamine (visco-supplementation) had a chondro-protective effect in the ACLT model compared with sham controls.
28. Papaioannou N, Krallis N, Triantafillopoulos I, et al. Optimal timing of research after anterior cruciate ligament resection in rabbits. *Contemp Top Lab Anim Sci* 2004;43:22–27. [PubMed: 15636551]
29. Hongbin W, Jingyuan D, Linyun C, et al. Carboxymethylated chitin reduces MMP-1 expression in rabbit ACLT osteoarthritic cartilage. *Ann Rheum Dis* 2004;63:369–372. [PubMed: 15020329]
- 30•. Hayami T, Pickarski M, Wesolowski GA, et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. *Arthritis Rheum* 2004;50:1193–1206. [PubMed: 15077302] Subchondral bone remodeling plays an integral part in osteoarthritis progression following ACLT in the rat. Inhibitors of bone resorption slowed disease progression.
31. Jo H, Ahn HJ, Kim EM, et al. Effects of dehydroepiandrosterone on articular cartilage during the development of osteoarthritis. *Arthritis Rheum* 2004;50:2531–2538. [PubMed: 15334467]
32. DeGroot J, Verzijl N, Wenting-van Wijk MJ, et al. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. *Arthritis Rheum* 2004;50:1207–1215. [PubMed: 15077303]
- 33•. Innes JF, Costello M, Barr FJ, et al. Radiographic progression of osteoarthritis of the canine stifle joint: a prospective study. *Vet Radiol Ultrasound* 2004;45:143–148. [PubMed: 15072147] Radiographic features of osteoarthritis (global assessment, effusion, and osteophytosis) increased with time out to 13 months following ACLT. Mild changes were noted in the unoperated control knee as well.

34. Lajeunesse D, Martel-Pelletier J, Fernandes JC, et al. Treatment with licofelone prevents abnormal subchondral bone cell metabolism in experimental dog osteoarthritis. *Ann Rheum Dis* 2004;63:78–83. [PubMed: 14672896]
35. Pelletier JP, Boileau C, Brunet J, et al. The inhibition of subchondral bone resorption in the early phase of experimental dog osteoarthritis by licofelone is associated with a reduction in the synthesis of MMP-13 and cathepsin K. *Bone* 2004;34:527–538. [PubMed: 15003800] Treatment with licofelone decreased morphological changes in subchondral bone and reduced the levels of MMP-13, slowing osteoarthritis progression in a dose-dependent manner in the ACLT model.
36. Rogachefsky RA, Altman RD, Markov MS, et al. Use of a permanent magnetic field to inhibit the development of canine osteoarthritis. *Bioelectromagnetics* 2004;25:260–270. [PubMed: 15114635] Using the ACLT model, it was determined that exposure to a magnetic field may have chondroprotective effects.
37. Alhadlaq HA, Xia Y, Moody JB, Matyas JR. Detecting structural changes in early experimental osteoarthritis of tibial cartilage by microscopic magnetic resonance imaging and polarised light microscopy. *Ann Rheum Dis* 2004;63:709–717. [PubMed: 15140779] Found that the total cartilage thickness increases in the early stages of osteoarthritis following ACLT, while the thickness of the superficial zone decreases.
38. Pond MJ, Nuki G. Experimentally induced osteoarthritis in the dog. *Ann Rheum Dis* 1973;32:387–388. [PubMed: 4726075]
39. Brandt KD, Braunstein EM, Visco DM, et al. Anterior (cranial) cruciate ligament transection in the dog: a bona fide model of osteoarthritis, not merely of cartilage injury and repair. *J Rheumatol* 1991;18:436–446. [PubMed: 1856812]
40. Smith, MM.; Ghosh, P. Osteoarthritis: diagnosis and medical/surgical management. 3rd ed.. WB Saunders; Philadelphia: 2001. Experimental models osteoarthritis; p. 171-200.
41. Comerford EJ, Tarlton JF, Innes JF, et al. Metabolism and composition of the canine anterior cruciate ligament relate to differences in knee joint mechanics and predisposition to ligament rupture. *J Orthop Res* 2005;23:61–66. [PubMed: 15607876]
42. Lohmander LS, Ionescu M, Jugessur H, et al. Changes in joint cartilage aggrecan after knee injury and in osteoarthritis. *Arthritis Rheum* 1999;42:534–544. [PubMed: 10088777]
43. Beynon BD, Uh BS, Fleming BC, et al. Rehabilitation following anterior cruciate ligament reconstruction: a prospective, randomized, double-blind comparison of accelerated versus non-accelerated rehabilitation. *Am J Sports Med* 2005;33:347–359. [PubMed: 15716250] Aggrecan turnover, collagen synthesis, and collagen degradation are elevated following ACL reconstruction, suggesting that the cartilage metabolism is abnormal (prospective randomized controlled trial).
44. Pinczewski LA, Deehan DJ, Salmon LJ, et al. A five-year comparison of patellar tendon versus four-strand hamstring tendon autograft for arthroscopic reconstruction of the anterior cruciate ligament. *Am J Sports Med* 2002;30:523–536. [PubMed: 12130407]
45. Spindler KP, Kuhn JE, Freedman KB, et al. Anterior cruciate ligament reconstruction autograft choice: bone-tendon-bone versus hamstring: does it really matter? A systematic review. *Am J Sports Med* 2004;32:1986–1995. [PubMed: 15572332]
46. Daniel DM, Stone ML, Dobson BE, et al. Fate of the ACL-injured patient: a prospective outcome study. *Am J Sports Med* 1994;22:632–644. [PubMed: 7810787]
47. Johma NM, Borton DC, Clingeleffer AJ, Pinczewski LA. Long term osteoarthritic changes in anterior cruciate ligament reconstructed knees. *Clin Orthop* 1999;358:188–193. [PubMed: 9973991]
48. Fink C, Hoser C, Benedetto KP. Development of arthrosis after rupture of the anterior cruciate ligament: a comparison of surgical and conservative therapy. *Unfallchirurg* 1994;97:357–361. [PubMed: 7939737]
49. Fink C, Hoser C, Hackl W, et al. Long-term outcome of operative or nonoperative treatment of anterior cruciate ligament rupture – is sports activity a determining variable? *Int J Sports Med* 2001;22:304–309. [PubMed: 11414676]
50. Jones HP, Appleyard RC, Mahajan S, Murrell GA. Meniscal and chondral loss in the anterior cruciate ligament injured knee. *Sports Med* 2004;33:1075–1089. [PubMed: 14599234] A comprehensive review article focusing on the influence of meniscal, chondral, and subchondral bone injuries on the ACL-deficient knee.

51. Fithian DC, Paxton LW, Goltz DH. Fate of the anterior cruciate ligament-injured knee. *Orthop Clin North Am* 2002;33:621–636. [PubMed: 12528905]
52. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* 2004;42:1–9. [PubMed: 15049520]
53. Bramono DS, Richmond JC, Weitzel PP, et al. Matrix metalloproteinases and their clinical applications in orthopaedics. *Clin Orthop* 2004;428:272–285. [PubMed: 15534553]
54. Karachalios T, Zibis A, Papanagiotou P, et al. MR imaging findings in early osteoarthritis of the knee. *Eur J Radiol* 2004;50:225–230. [PubMed: 15145481]
55. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. *Arthritis Rheum* 2004;50:2811–2819. [PubMed: 15457449]
- 56••. Andriacchi TP, Mundermann A, Smith RL, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng* 2004;33:447–457. [PubMed: 15095819] Introduces a mechanical mechanism for the onset and progression of osteoarthritis that applies to the ligament-injured patient (review article).
- 57••. Andriacchi TP, Dyrby CO. Interactions between kinematics and loading during walking for the normal and ACL deficient knee. *J Biomech* 2005;38:293–298. [PubMed: 15598456] Abnormal kinematics in the ACL-deficient knee demonstrated during gait were most notable near heel strike. The tibia was internally rotated throughout the gait cycle.
58. Carter DR, Beaupre GS, Wong M, et al. The mechanobiology of articular cartilage development and degeneration. *Clin Orthop* 2004;427:S69–S77. [PubMed: 15480079]
- 59•. Yamamoto Y, Hsu WH, Woo SL-Y, et al. Knee stability and graft function after anterior cruciate ligament reconstruction: a comparison of a lateral and an anatomical femoral tunnel placement. *Am J Sports Med* 2004;32:1825–1832. [PubMed: 15572308] Graft placement will influence tibiofemoral kinematics following ACL reconstruction when using a two-bundle technique.
- 60••. Jonsson H, Riklund-Ahlstrom K, Lind J. Positive pivot shift after ACL reconstruction predicts later osteoarthritis: 63 patients followed 5-9 years after surgery. *Acta Orthop Scand* 2004;75:594–599. [PubMed: 15513493] Abnormal subchondral bone metabolism is observed in patients following ACL reconstruction, and this is dependent on the degree of joint stability (longitudinal cohort study).
- 61••. Logan MC, Williams A, Lavelle J, et al. Tibiofemoral kinematics following successful anterior cruciate ligament reconstruction using dynamic multiple resonance imaging. *Am J Sports Med* 2004;32:984–992. [PubMed: 15150047] Demonstrated that the lateral compartment contact position of the ACL-reconstructed knee is approximately 5 mm anterior to that of the ACL intact knee. Abnormal kinematics may predispose ACL-reconstructed patients to osteoarthritis.
- 62•. Logan M, Dunstan E, Robinson J, et al. Tibiofemoral kinematics of the anterior cruciate ligament (ACL)-deficient weightbearing, living knee employing vertical access open ‘interventional’ multiple resonance imaging. *Am J Sports Med* 2004;32:720–726. [PubMed: 15090390] Injury to the ACL causes an anterior shift of the lateral tibial compartment during weight-bearing. Abnormal kinematics may predispose ACL-injured patients to osteoarthritis.
63. Woo SL-Y, Kanamori A, Zeminski J, et al. The effectiveness of reconstruction of the anterior cruciate ligament with hamstrings and patellar tendon – a cadaveric study comparing anterior tibial and rotational loads. *J Bone Joint Surg Am* 2002;84:907–914. [PubMed: 12063323]
- 64••. Tashman S, Collon D, Anderson K, et al. Abnormal rotational knee motion during running after anterior cruciate ligament reconstruction. *Am J Sports Med* 2004;32:975–983. [PubMed: 15150046] The kinematics of the ACL-reconstructed knee are abnormal following ACL reconstruction. Patients run with their knees externally rotated and more adducted than their contralateral control knees. Abnormal kinematics may predispose ACL-reconstructed patients to osteoarthritis.
65. Yagi M, Wong EK, Kanamori A, et al. Biomechanical analysis of an anatomic anterior cruciate ligament reconstruction. *Am J Sports Med* 2002;30:660–666. [PubMed: 12238998]
66. Williams GN, Snyder-Mackler L, Barrance PJ, et al. Neuromuscular function after anterior cruciate ligament reconstruction with autologous semitendinosus-gracilis graft: analysis of muscle and tendon morphometry with magnetic resonance imaging. *J Bone Joint Surg Am* 2004;86:1936–1945. [PubMed: 15342756]

67. Williams GN, Barrant PJ, Snyder-Mackler L, Buchanan TS. Altered quadriceps muscle control in people with anterior cruciate ligament deficiency. *Med Sci Sports Exerc* 2004;36:1089–1097. [PubMed: 15235310]
68. Williams GN, Buchanan TS, Barrant PJ, et al. Quadriceps weakness, atrophy, and activation failure in predicted noncopers after anterior cruciate ligament injury. *Am J Sports Med* 2005;33:402–407. [PubMed: 15716256]
69. Kobayashi M, Squires GR, Mousa A, et al. Role of interleukin-1 and tumor necrosis factor alpha in matrix degradation of human osteoarthritic cartilage. *Arthritis Rheum* 2005;52:128–135. [PubMed: 15641080] The inhibition of some of the cytokines released during the inflammation response may retard osteoarthritis progression.
70. Hogervorst T, Rijcken THP, Rucker D, et al. Changes in bone scans after anterior cruciate ligament reconstruction – a prospective study. *Am J Sports Med* 2002;30:823–833. [PubMed: 12435648]
71. Johnson DL, Bealle DP, Brand JC, et al. The effect of a geographic lateral bone bruise on knee inflammation after acute anterior cruciate ligament rupture. *Am J Sports Med* 2000;28:152–155. [PubMed: 10750989]
72. Davies NH, Niall D, King LJ, et al. Magnetic resonance imaging of bone bruising in the acutely injured knee – short-term outcome. *Clin Radiol* 2004;59:439–445. [PubMed: 15081849] Bone bruises persist for at least 12–14 weeks following an acute traumatic ligament injury (observational cohort study).
73. Dimond PM, Fadale PD, Hulstyn MJ, et al. A comparison of MRI findings in patients with acute and chronic ACL tears. *Am J Knee Surg* 1998;11:153–159. [PubMed: 9728714]
74. Costa-Paz M, Muscolo ML, Ayerza M, et al. Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. *Arthroscopy* 2001;17:445–449. [PubMed: 11337710]
75. Doschak MR, Wohl GR, Hanley DA, et al. Antiresorptive therapy conserves some periarticular bone and ligament mechanical properties after anterior cruciate ligament disruption in the rabbit knee. *J Orthop Res* 2004;22:942–948. [PubMed: 15304263] Bisphosphonates administered after ACLT was shown to conserve some subchondral bone changes and slowed osteoarthritis progression.
76. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2005;18CD005321
77. Butler DL, Shearn JT, Juncosa N, et al. Functional tissue engineering parameters toward designing repair and replacement strategies. *Clin Orthop* 2004;427(suppl):S190–S199. [PubMed: 15480066] An excellent review article on the current state of tissue engineering for the treatment of soft tissue injuries.
78. Hunziker EB. Articular cartilage repair: basic science and clinical progress: a review of the current status and prospects. *Osteoarthritis Cartilage* 2002;10:432–463. [PubMed: 12056848]
79. Roos EM, Dahlberg L. Physical activity as medication against arthrosis – training has a positive effect on the cartilage. *Lakartidningen* 2004;101:2178–2181. [PubMed: 15281305]
80. Cibere J, Thorne A, Kopec JA, et al. Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers. *J Rheumatol* 2005;32:896–902. [PubMed: 15868627]
81. Bruyere O, Honore A, Ethgen O, et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression: results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. *Osteoarthritis Cartilage* 2003;11:1–5. [PubMed: 12505481]
82. Tiraloche G, Girard C, Chouinard L, et al. Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. *Arthritis Rheum* 2005;52:1118–1128. [PubMed: 15818693] Oral administration of glucosamine slowed the progression of osteoarthritis in the ACLT model. The effect was most evident in the lateral femoral condyle.
83. Pascher A, Steinert AF, Palmer GD, et al. Enhanced repair of the anterior cruciate ligament by in situ gene transfer: evaluation in an in vitro model. *Mol Ther* 2004;10:327–336. [PubMed: 15294179]
84. Hewett TE, Myer GD, Ford KR. Reducing knee and anterior cruciate ligament injuries among female athletes: a systematic review of neuromuscular training interventions. *J Knee Surg* 2005;18:81–88.

Figure 1.

Onset and progression of osteoarthritis

Many factors are thought to contribute to the onset and progression of osteoarthritis following a ligament injury; however, the mechanisms responsible remain unknown. Factors such as mechanical instability may alter cartilage metabolism, which in turn causes cartilage breakdown, leading to arthritis.

Figure 2.

Concentrations of biomarkers of articular cartilage metabolism from synovial fluid after anterior cruciate ligament reconstruction suggest that the articular cartilage undergoes metabolic changes

For example, the concentration of the marker for aggrecan turnover (the 846-epitope) was elevated relative to the control knee (solid line) over the first 12 months and then approached that of normal by 24 months. It is unknown whether this marker will remain at the normal levels or continue to drop with time. Adapted with permission [43••].

Figure 3.
Plausible mechanical mechanism for the onset and progression of osteoarthritis following ligament injury
Reproduced with permission [56••].