ABSTRACT
Post-traumatic osteoarthritis (PTOA) occurs as a consequence of joint trauma or occupations or sports that subject joints to excessive loading stresses. Ligament injuries to the knee, particularly tears of the anterior cruciate ligament (ACL), often result in PTOA. Approximately half of the individuals with an ACL injury develop PTOA regardless of the reconstruction of the torn ligament. This observation has raised the possibility that other injuries occur to the knee in association with ACL tears that may involve ligamentous capsular structures, articular cartilage, or subchondral bone. Many ACL injuries occur in noncontact sports and are the result of biomechanical abnormalities. Female athletes are more likely than their male counterparts to suffer ACL injuries. This review outlines the epidemiology of ACL tears, its pathology in cartilage and bone, some of the demographic, biomechanical, and neuromuscular factors involved in ACL tears, and PTOA and important information gained from preclinical injury models.

KEYWORDS: Osteoarthritis, Ligament Injury, Arthroscopy

INTRODUCTION
Post-traumatic osteoarthritis (PTOA) often follows joint fractures and dislocations, ligament and cartilage injuries, and chronic ligament instability among other traumatic affections of joints, and occupations or sports that subject joints to high levels of impact and torsional loading. Individuals experiencing significant ligamentous-capsular or meniscal injuries to the knee have a 10-fold increased risk of PTOA compared to uninjured persons. The commonest ligament injury to the knee resulting in PTOA is tear of the anterior cruciate ligament (ACL) (Figure 1). Athletes, from recreational to professional levels are more likely to suffer from an ACL injury, which in turn, can lead to a discontinuation of their athletic activity, career, and costly medical expenses. It has been reported that knee injuries account for 60% of all sports-related surgeries, while 50% of those knee injuries are ACL related. This is a particularly troubling etiologic association because it commonly occurs in a young population and places them at high risk for PTOA. Between 100,000 and 400,000 ACL injuries occur annually in the United States with 100,000 ACL reconstructive procedures performed each year. Approximately 50% of individuals with an ACL injury develop PTOA 10-15 years after injury regardless of treatment of the ligament injury. In all likelihood, both types of injuries frequently occur together, and injury to cartilage or subchondral bone may occur at the time of ACL tear not be apparent to the clinician at the time of injury. In a 14-year follow-up study of 205 male athletes with ACL tears, 78% had degenerative signs in their injured knee compared to 4% in their uninjured knee. These findings were confirmed by a study that found that the incidence of chondropathy determined by MRI was 92.94%. A significant decrease in the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) index, reflecting loss of cartilage extracellular matrix (aggrecan) in ACL-injured knees, has been demonstrated. Considered together, these data suggest that chondral injury co-exists with ACL injury and contributes to PTOA. Figure 2 displays types of cartilage injuries that occur with ACL tears including meniscal tears, debris synovitis, cartilage damage, and injury to the subchondral bone. It appears that, irrespective of surgical treatment, patients with ACL injuries develop PTOA for reasons that are poorly understood.
Several studies have demonstrated impaction injuries of cartilage and subchondral bone with ACL tears, some severe enough to cause fracture and bone marrow edema persisting for up to one year in 60% of injured knees. Bone marrow edema, termed by some “bone marrow lesions,” can occur in more than 80% of cases of ACL injuries. Recent studies have shown that subchondral bone marrow edema lesions are associated with pain and progression of cartilage degradation. Bone marrow edema is characterized by high signal intensity on T2 sequences of MRI images. Histologically, bone marrow edema lesions are distinguished by marrow necrosis, abnormal trabeculae and reduced mineral density. Some studies have shown intraosseous hypertension. Figure 2 presents a typical appearance of bone marrow lesions. Certainly there is suggestive clinical evidence that occult bone lesions occur with ACL injury and contribute to PTOA.

Pathology of Articular Cartilage

Pathologic changes in articular cartilage extracellular matrix and chondrocytes have been described within 48 hours after impaction trauma consisting of loss of extracellular matrix molecules, fibrillation, fissuring, clefting, chondrocyte cloning, vascular violation of the tide mark, loss of lubricin, damage to collagen, and are proportional to the extent of impact energy. Cellular changes include apoptosis and cell death. In vitro models confirm the presence of chondrocyte necrosis and apoptosis initiated at a load of approximately 25 megapascal (MPa). Lower loads do not produce structural damage, but do produce cell death indicating that chondrocyte necrosis can precede structural damage with loads as low as 3MPa. Lower levels of repetitive compressive injuries can accumulate enough degradative changes over time to cause reductions in mechanical properties similar to higher levels of injury by up-regulating the synthesis of matrix degrading enzymes. End stage PTOA is characterized by loss of articular cartilage and exposure of subchondral bone (Figure 4).

Pathophysiology of Subchondral Bone

Understanding the role of subchondral bone in the pathophysiology of PTOA remains elusive. In particular, the role of the osteoblasts in subchondral bone remodeling and cartilage breakdown remains unclear, as does the significance of recent descriptions of bone marrow edema and altered perfusion. Osteoblasts alter their cytokine expression profile in response to their physicochemical environment and changes in the physical environment in subchondral bone in PTOA are well within the range in which osteoblasts are sensitive. Intraosseous hypertension produced experimentally by venous ligation results in the histopathological hallmarks of PTOA – focal avascular necrosis (AVN), trabecular remodeling, thickening of the subchondral bone plate, endosteal and periosteal new bone formation and sclerosis. Several observations have suggested that intraosseous hypertension is caused by increased venous resistance resulting in outflow obstruction and venous stasis. The pathophysiological consequences of intraosseous hypertension may lie in its association with diminished perfusion and hypoxia which could serve as parts of a signaling complex to osteoblasts. Osteoblasts are responsive to hypoxia and this may be involved in mechanotransduction pathways. Osteoblasts subjected to hypoxic conditions with $pO_2$ of 35-40mmHg, markedly alter the expression of...
profile of growth factors associated with the pathologic findings of OA, increased bone remodeling and cartilage degradation. Osteoblasts derived from OA bone also express high levels of alkaline phosphatase, osteocalcin, and IGF-1 which are related to bone remodeling.

### BIOMECHANICAL AND NEUROMUSCULAR FACTORS IN ACL TEARS

Sports medicine researchers and clinicians have focused on biomechanical risk factors for injuries and preventative measures. Studies have examined extrinsic risk factors including the level of sport (training versus competition), shoe type, and playing surface, and intrinsic risk factors such as age, gender, and even hormonal status. The most frequent mechanisms of ACL injuries in sports, almost 70%, are non-contact.[14] Non-contact ACL injuries include stopping mid-stride to respond to an opponent’s change in direction, especially in soccer, and an increase in landing from jumping, such as in basketball. Studies of neuromuscular and biomechanical factors have shown that many ACL injuries are not the results of contact and that distinct biomechanical patterns such as excessive coronal plane motion, less knee flexion, and landing flatfooted are associated with ACL injury.[15] These observations suggest that ACL injuries, especially in females, are primarily neuromuscular and biomechanical in nature and subject to modification.

Female athletes in particular, are more likely to incur ACL injuries than male athletes. Over the past two decades there has been a marked increase in ACL injuries in young female athletes in sports that involve cutting, jumping, and pivoting.[15] One study looked at the effect of gender on injury rates among military recruits during basic training (n=861) and found that women had twice as many injuries as men (relative risk = 2.1, 95% CI = 1.78 to 2.5).[16] Another study looked at ACL injuries among male and female recruits playing intercollegiate sports, coed intramural sports, and military training, and found a combined relative risk of 2.44 for women compared with men.[17] This has been ascribed to increased valgus movements during landing, hormone levels, narrower intercondylar notch width, and smaller AC ligaments.[14,18] Neuromuscular training programs suggest that enhancing body control may decrease ACL injuries in women.[18] It has been found that male athletes attenuate knee ligament stresses during jumping by knee flexion and absorption of strain by the quadriceps. By contrast, female athletes have been found to land with the knee relatively straighter with more stress taken up by the ACL. These relatively higher stresses are believed to contribute to ACL injuries. Programs have been devised to train female athletes to attenuate more stress with their quadriceps, thus reducing load, and hopefully injury, to the ACL. Prevention programs that involve proprioception, plyometrics, strength training, and improved jumping, stopping, and turning techniques are showing promising results.[18] With this type of training, female athletes have been shown to reduce coronal plane motion, exert more muscular control, and reduce ACL stresses during movements such as jumping, landing, pivoting, and deceleration.

### PRECLINICAL INJURY MODELS

Preclinical injury models are useful for several reasons; 1.) Human tissue is unavailable for study except in end-stage PTOA, 2.) Dosimetry of impact can be determined and related to pathological changes in cartilage and bone, 3.) Sequential histopathological examinations of joints can reveal the time course and magnitude of progressive development of PTOA. The fracture threshold for the femoral condyle in rabbits has been reported to be about 120MPa and most direct impaction injury studies have used magnitudes between 20-50MPa to produce chondrocyte death and loss of extracellular matrix integrity. Models of impaction injury to cartilage and bone have been established in rabbits, dogs, and sheep in vivo, as well as in vitro explants and changes typical of PTOA have been demonstrated. In vitro studies have reported that cell death and concomitant extracellular matrix damage are initiated at stress magnitudes of 15 to 25 MPa.[19] A stress magnitude >40 MPa has caused complete cell death under the impacted region. One key in vitro study determined the effects of stress magnitude on cartilage extracellular matrix damage and cell viability in the rabbit knee. Femoral condyles were impacted with stress magnitudes of 15-50MPa at a stress rate of 420MPa/s. The stress rate was based on predictions of joint impact that may occur in contact sports, joint injuries, and ACL tears. All specimens impacted with peak stresses >35MPa showed visible surface damage in the impacted region. Superficial matrix damage was observed in 2 of 4 specimens impacted with peak stresses between 30 to 35MPa. Below 30MPa there was no visible matrix damage. A limitation of in vitro models is that it is not possible to investigate the cartilage mechanobiologic response to injury over time.[20]

Using a novel in vivo animal test system that is capable of independently applying quantifiable, precise stress magnitudes and rates to the femoral condyle of the rabbit knee, PTOA has been induced as a result of a single impact trauma to the articular cartilage and subchondral bone.[20] The extent of cell death depends on the magnitude of the impact at the time of injury. Initial cartilage injuries progress to almost complete cartilage matrix and chondrocyte loss throughout the depth of the impacted region by 3 weeks after impact. The post impact morphological biochemical observations are similar to early-to-late stage pathologic observations typically seen in human PTOA. In an important series of in vivo studies, the femoral condyle was impacted with a peak stress of 35MPa at a stress rate of 420MPa/s. Zero-time rabbits had histologic evidence of matrix damage patterns consisting of surface roughening and distinct cracks that propagated to 20% of the depth. Histologic sections of rabbits sacrificed
at 3 weeks after impact revealed substantial surface damage with almost complete cell loss and reduced Safranin-O staining throughout the depth of the articular cartilage that was confined to the impacted site. Threshold stress at which articular cartilage damage occurs as 25MPa at a stress rate of 420MPa/sec, corresponding to in vivo joint impact stress and rate commonly seen in traumatic joint injuries and sports. Cartilage responses to various loads have been reported.[21]

Table 1.

<table>
<thead>
<tr>
<th>Load (MPa)</th>
<th>Response</th>
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<tbody>
<tr>
<td>10</td>
<td>No Chondrocyte Death</td>
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<tr>
<td>20</td>
<td>No Chondrocyte Death</td>
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<tr>
<td>35</td>
<td>50% Chondrocyte Death and Surface Fissures</td>
</tr>
<tr>
<td>50</td>
<td>100% Chondrocyte Death and Gross Matrix Damage</td>
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**ARTHITIS FOUNDATION ACL/PTOA RESEARCH INITIATIVE**

The national Arthritis Foundation is developing an ACL Intervention Initiative with the hopes of discovering disease-modifying therapies. The human ACL PTOA model will be used to study the onset and progression of OA. The specific goals of the Arthritis Foundation's ACL Intervention Initiative are:

- Determining the causes of PTOA
- Exploring biomarkers of PTOA
- Identifying individuals at risk for developing PTOA
- Developing diseases modifying pharmacological and other treatments

To achieve these goals, the Arthritis Foundation has committed $2.3M in 2012 for PTOA research ranging from the identification of biomarkers to imaging techniques. In 2013, the Arthritis Foundation has committed $1M to the ACL Intervention Initiative [Arthritis Foundation-personal communication].

**References**


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