17 Sports Medicine
GUEST EDITORS: ROY K. AARON, MD; JENNIFER R. RACINE, BA; ROBERT M. SHALVOY, MD

R.K. Aaron, MD

18 The Female Athlete Triad
ELIZABETH HORN, MD; NICOLE GERGEN, MD; KELLY A. MCGARRY, MD, FACP

K.A. McGarry, MD

22 Exercise-Induced Rhabdomyolysis
GEORGE LEE, MD

G. Lee, PhD

25 Post-Traumatic Osteoarthritis after ACL Injury
JENNIFER R. RACINE, BA; ROY K. AARON, MD

J.R. Racine, BA

29 Predicting Success in ACL Reconstruction
ROBERT M. SHALVOY, MD

R.M. Shalvoy, MD
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Sports Medicine

ROY K. AARON, MD; JENNIFER R. RACINE, BA; ROBERT M. SHALVOY, MD
GUEST EDITORS

Athletic training and sports-related injuries can involve multiple organ systems. Examples include exercise-induced asthma, idiopathic hypertrophic subaortic stenosis [hypertrophic cardiomyopathy], and fluid and electrolyte imbalance. In this issue of the Rhode Island Medical Journal, we present examples of sports-related pathology reflecting multiple organ involvement. “The Female Athlete Triad” describes the effects of exercise on both the endocrine system and bone density. Female athletes are susceptible to menstrual dysfunction and loss of bone density associated with negative energy balance. Originally thought to occur in women with eating disorders, it is now recognized to occur with normal caloric intake in the face of excessive caloric demands of exercise.

“Exercise Induced Rhabdomyolysis” describes the syndrome of skeletal muscle breakdown associated with strenuous exercise. The clinical presentation consists of disproportionate muscle pain after exercise associated with elevated creatine phosphokinase. The mechanism seems to be related to cell membrane damage with intracellular influx of calcium and efflux of cellular breakdown products. In extreme cases, myoglobinuria and acute renal failure result.

Osteoarthritis (OA) following joint injuries in athletics [post-traumatic OA] is now recognized as a whole joint disease involving multiple tissues – cartilage, bone, ligament, capsule, and possibly having contributions from bone vasculature and inflammatory pathways. Anterior cruciate ligament tears are common causes of post-traumatic OA but most certainly involves trauma to other tissues in the joint that may be unrecognized at the time of injury.

“Post-traumatic Osteoarthritis after ACL Injury” discusses the contributions of bone and cartilage to joint damage and describes the mechanics of injury in pre-clinical models. Epidemiological and clinical research initiatives that may result in treatment programs are described.

Contemporary knee ligament reconstructions are assisted by intraoperative computer guidance for optimal graft placement and tension. “Predicting Success in ACL Reconstruction” describes the challenges of individualizing reconstructions and optimizing knee stability. The role of state-of-the-art computer navigation for the assessment and correction of the ACL injury is described along with the functional outcomes and return to sports of ACL-injured athletes.

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The Female Athlete Triad
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ABSTRACT
The female athlete triad is a spectrum of interrelated pathophysiologic consequences of low energy availability, menstrual dysfunction, and low bone mineral density. Components of the triad are not only counterproductive to athletic performance goals, but can lead to serious long-term negative health outcomes. Practitioners caring for female athletes play an important role detecting at-risk athletes early in their course along the disease spectrum. Importantly, women who are evaluated for one component of the triad should always be screened for the other two. Detecting the disorder early is the most important factor for preventing the potentially severe consequences, and requires heightened vigilance on the part of all those who work with this special patient population. In this article, we discuss the epidemiology, pathophysiology, diagnosis, evaluation, and management of the female athlete triad.

KEYWORDS: female athlete triad, menstrual dysfunction, disordered eating, altered bone density

INTRODUCTION
Female involvement in athletics and exercise has increased over recent decades. While exercise is encouraged for general health and disease prevention, female athletes are susceptible to negative health outcomes if energy balance is not maintained. Physicians should be familiar with the female athlete triad to enable proper evaluation, diagnosis, and management of the disorder.

DEFINITION
The female athlete triad is a spectrum of disease encompassing a broad set of disorders involving low energy availability, menstrual dysfunction, and low bone mineral density (BMD). First identified by the American College of Sports Medicine (ACSM) in 1992, the triad was initially characterized by disordered eating, amenorrhea, and osteoporosis. Since then, the nosology has been modified to reflect the disease continuum. The current definition reflects variable manifestations within each component of the triad. For example, negative energy balance can occur in athletes with average caloric intake but excessive energy expenditure, or in those with eating disorders. Menstrual dysfunction includes primary amenorrhea, secondary amenorrhea, and oligomenorrhea. Low BMD may manifest as an asymptomatic finding on dual-energy X-ray absorptiometry (DEXA) scan, stress fractures, or pathologic fractures. Fundamentally, the female athlete triad is a spectrum of three distinct pathophysiologic states with varied presentations.

EPIDEMIOLOGY
A recent review examining young women ages 17–25 years old who exercise suggested that the prevalence of all three components of the disorder ranged between 0-15.9%. The wide prevalence estimates are due to several factors, including the changing definition of the female athlete triad, variance in prevalence between types of athletes, as well as inherent diagnostic challenges. It is uncommon for all components of the triad to be diagnosed in concert. Rather, women afflicted with the female athlete triad evolve symptoms and features of the syndrome along non-congruent disease continuums for each component of the triad. Women participating in “lean sports” which assign aesthetic value to performance including gymnastics, ballet dancing, and ice skating are at higher risk for developing the female athlete triad. Studies comparing lean-sport athletes versus non-lean sport athletes demonstrated a prevalence of all three components of the female athlete triad in up to 6.7% of lean-sport athletes compared to 2.0% of non-lean sport athletes. Epidemiological data exist for components of the female athlete triad. Negative energy balance is the primary disorder in the female athlete triad driving menstrual dysregulation and low BMD. Low energy availability can occur in the setting of both caloric restriction and excessive exercise. In the general adolescent female population, the prevalence of disordered eating is estimated between 13-20%. By contrast, between 15% and 62% of female high school and college athletes exhibit disordered eating, but it is unclear how many have clinical eating disorders or low energy availability leading to triad sequelae. Menstrual dysfunction manifesting as secondary amenorrhea is reported as high as 69% prevalence in female athletes who participate in lean sports compared with 5% of the general population. The prevalence of low BMD is difficult to define in the female athlete population as most young women are not candidates
Pathophysiology: Low Energy Availability

Low energy availability, defined as insufficient energy to supply metabolic demand, is the primary disorder driving pathophysiologic changes in the female athlete triad. Negative energy balance results in insufficient metabolic supply for normal menstrual function, bone development, and bone maintenance. Factors dictating energy availability include caloric intake, baseline metabolic function, and energy expenditure.

Female athletes may maintain adequate nutrition for average caloric requirements but rigorous training demands contribute to caloric deficit. Alternatively, maladaptive dietary habits such as restriction, purging, laxative, stimulant and diuretic use may lead to insufficient energy availability. When evaluating the female athlete triad, it is important to distinguish between excessive energy expenditure for caloric intake, disordered eating, and a clinically defined eating disorder, the latter of which would necessitate psychiatric evaluation.

Pathophysiology: Menstrual Dysfunction

Menstrual dysfunction may present as primary amenorrhea, secondary amenorrhea, or oligomenorrhea. Primary amenorrhea is the absence of menses at age 15 in the presence of normal growth and secondary sexual characteristics or the absence of menses three years after development of secondary sexual characteristics. Secondary amenorrhea is the absence of menses for more than three cycles or six months in women who previously had regular menses, or the absence of menses for more than nine months in women who previously had irregular menses. Oligomenorrhea is defined as menstrual cycles >35 days apart. Because eumenorrhea may not be established until late in adolescence or early adulthood, menstrual dysfunction may be difficult to establish.

When a female athlete develops negative energy balance and subsequent hypometabolic state, hypothalamic GnRH pulsatility is altered. Hypothalamic dysfunction leads to anovulation and subsequent menstrual disturbances.

Pathophysiology: Altered Bone Mineral Density

Bone health is maintained through a continuous process of balanced osteoblastic and osteoclastic activity. In females with a negative energy balance, altered GnRH pulsatility suppresses the hypothalamic-pituitary axis and results in a hypoestrogenic state. In healthy menstruating females, estrogen suppresses osteoclastic activity, promoting bone development and normal BMD. Thus, low BMD in women with the female athlete triad is secondary to the lack of adequate estrogen supply for optimal bone health. Women with menstrual dysfunction and low estrogen can lose up to 2% of BMD annually. Rigorous athletic activity alters the development and maintenance of bone health in preferential anatomic locations. In female athletes, sport activity may increase density of weight bearing bones such as the femur while other bones, including the spine may demonstrate altered BMD. Pathologic and stress fractures should prompt clinical evaluation for the female athlete triad.

Diagnostic Evaluation: The Female Athlete Triad

Primary care providers play an integral role in the diagnosis of the triad. Identifying at-risk athletes optimally occurs during academic and sports related screenings or in the setting of office visits for menstrual dysfunction, pathologic or stress fractures or disordered eating. Ideally, parents and athletic trainers should be able to recognize components of the female athlete triad and its negative health consequences.

Assessing Low Energy Availability

Evaluation of energy state is essential in evaluating a patient for the female athlete triad. Important historical aspects include dietary habits (current and past), highest and lowest weight, and perception of ideal body weight. Patients should be assessed for disordered eating including restriction,
purging, and use of diuretics, laxatives, or stimulants. Activity level should be determined by evaluating duration and intensity of daily exercise and sports involvement. Examination should include measurement of orthostatic vital signs assessing for resting tachycardia and volume depletion, weight, and BMI. It is important to note findings suggestive of eating disorders including lanugo, parotid gland enlargement, dental enamel erosions and knuckle calluses caused by self-induced vomiting. Laboratory evaluation should include complete blood counts, complete metabolic profile, thyroid function tests and urinalysis. If electrolyte abnormalities are present or the patient presents with bradycardia, an EKG should be performed to assess for arrhythmia or prolonged QT interval.

Menstrual Dysfunction
The ACSM recommends screening for the triad in any female athlete with a total of six months of amenorrhea or oligomenorrhea. When evaluating a patient for menstrual dysfunction, providers should ask about age at menarche, frequency and duration of menstrual cycles, last menstrual period, and medication use including oral contraceptives. Careful examination of the patient with a focus on secondary sexual characteristics, signs of hyperandrogenism or findings suggestive of thyroid dysfunction may help distinguish other causes of menstrual dysfunction from altered GnRH pulsatility seen in the female athlete triad. The first step in laboratory evaluation is a pregnancy test. Subsequent work up may include evaluation for polycystic ovarian syndrome, thyroid or pituitary abnormalities. Drugs which affect the menstrual cycle such as contraceptives, antidepressants or thyroid medications should be identified. Depending on the clinical scenario, evaluation of follicle stimulating hormone (FSH), leutinizing hormone (LH) and possibly MRI evaluation for a pituitary process may be indicated. Importantly, hypothalamic amenorrhea due to decreased GnRH pulsatility seen in the female athlete triad is a diagnosis of exclusion.

Altered Bone Mineral Density
Altered BMD may present as abnormal bone development, osteopenia, and osteoporosis. Initial evaluation should include obtaining a history of stress fractures, overuse injuries, and pathologic fractures. A careful assessment of ovulatory status should be performed. The evaluation of BMD can be difficult in the female athlete given continued bone development in adolescence. Osteoporosis can be evaluated with DEXA scanning using the T-score or the Z-score. The T-score compares BMD to a thirty year old adult control whereas the Z-score compares BMD to age and gender matched controls. The latter is a more appropriate diagnostic method for female athletes who have yet to achieve maximum bone density. Evaluation of osteoporosis in the young female athlete is further complicated by site dependent alteration in BMD as discussed previously.

TREATMENT CONSIDERATIONS

Low Energy State
Due to increased caloric requirements of female athletes, nutritional support and dietary counseling are integral to the treatment of these patients, regardless of the presence or absence of disordered eating. The ACSM recommends establishing weight goals in writing in order to continue athletic participation. Realistic training goals should be identified. Additionally, the organization recommends a nutrition education program, stress reduction, and consideration of bone densitometry screening. If there is concern for an eating disorder, referral to a mental health specialist is appropriate.

Menstrual Dysfunction
While a weight or energy requirement goal for the resumption of eumenorrhea has not been definitively established, one study found that restoration of eumenorrhea in anorexia nervosa patients required weight gain of 2 kilograms over the weight at which secondary amenorrhea occurred. Patients who wish to become pregnant require special consideration. While normalization of menstrual cycle and ovulation can be attained by increasing energy availability, weight gain, and subsequent normal pulsatile GnRH activity, other endocrinologic interventions are available and may be necessary but are beyond the scope of this article.

Altered Bone Mineral Density
The ACSM recommends consideration of DEXA screening in at risk patients. Resolving the low-energy state is the optimal treatment for altered BMD. A variety of therapies have been proposed. Bisphosphonates are used for the treatment of osteoporosis in post-menopausal women and have been considered in this disorder. Their effectiveness has yet to be demonstrated in premenopausal women. Human trials have not established bisphosphonate teratogenicity but animal trials have shown adverse effects on the fetus. A reasonable pharmacologic approach to bone health supplementation in the female athlete includes vitamin D (400-1000 IU/day) and calcium (1300 mg/day).

FUTURE RESEARCH
Future directions will include a focus on examining the role of hormone replacement in re-establishment of menstruation and normal BMD. Oral contraceptive pills have been used to treat adolescents with menstrual dysfunction from other causes, but their use has not been adequately studied in the female athlete population. Initial data in female athletes is mixed with respect to the effect of oral contraceptive pills on bone health. Transdermal estrogen is also an emerging area of research interest. It is thought that transdermal preparations of estrogen may be preferable to oral contraceptive pills in that they have less of an inhibitory effect on insulin-like growth factor-1, a trophic hormone that has been shown to promote bone formation. In
postmenopausal women, transdermal estrogen has reduced fracture risk, but its potential benefits and harms have not been well studied in the young female athlete population.

References

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Exercise-Induced Rhabdomyolysis
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ABSTRACT
Exercise-induced rhabdomyolysis, or exertional rhabdomyolysis (ER), is a clinical entity typically considered when someone presents with muscle stiffness, swelling, and pain out of proportion to the expected fatigue post exercise. The diagnosis is confirmed by myoglobinuria, and an elevated serum Creatinine Phosphokinase (CPK) level, usually 10 times the normal range. However, an elevation in CPK is seen in most forms of strenuous exercise, up to 20 times the upper normal range. Therefore, there is no definitive pathologic CPK cut-off. Fortunately, the dreaded complication of acute renal failure is rare compared to other forms rhabdomyolysis. We review the risks, diagnosis, clinical course and treatment for exercise-induced rhabdomyolysis.

KEYWORDS: exertional rhabdomyolysis, CPK, myoglobinuria, acute renal failure

INTRODUCTION
Rhabdomyolysis (RM) is a condition of striated muscle damage, usually in conjunction with an elevation in creatine phosphokinase (CPK). The mechanism involves either trauma or intracellular depletion of ATP leading to intracellular influx of calcium. This in turn results in the disruption of the cell membrane, and subsequent release of intracellular contents into the plasma and extracellular space. It is this translocation of intracellular debris that can potentially lead to serious complications, most notably acute renal failure (ARF). The incidence of acute renal failure complicating RM ranges from 15-50%. The most common causes of RM with resultant acute renal failure include ischemia, drugs, alcohol and trauma. Melli reported 475 hospitalized patients with RM at John Hopkins. Exogenous toxins, including illicit drugs, alcohol and medications were the most common cause, with an incidence of acute renal failure being 46%. The incidence of exercise-induced or exertional rhabdomyolysis (ER) in the general public is difficult to define, as many patients probably do not seek medical attention. However, data have been accrued from military recruits undergoing basic training. Wildly ranging rates have been described, due to the varying definitions utilized. The largest data set was by Hill, who reported, in a retrospective review of 574,688 U.S. Army soldiers, 1203 cases of ER or 0.2%. This translates to a yearly rate of 7-8 cases/10,000. Rates were higher men vs. women. Olerud et al., using serum myoglobin as a screening test, diagnosed ER in 40% of military recruits within the first 6 days of basic training.

DIAGNOSIS
The varying rate of ER is due to the nebulous diagnostic criteria. Clinically it can manifest itself with prolonged muscle swelling and tenderness, lasting several days longer than expected. Ensuing dark urine may develop, signifying myoglobinuria. Elevation of CPK is one of the main serologic criteria to define the entity. However, there is no defining set point in the height of the CPK rise to identify clinically relevant EH. A confounding factor is that CPK elevation after strenuous activity is quite common, with the range being quite variable. Thus, no normal post-exercise CPK value has been established. Studies in male marathoners and triathletes have demonstrated, 24 hours after race completion, CPK elevation in the several thousand range, 10-20 times the upper limit of normal. Of the exercises associated with ER, downhill running and those that induce eccentric (muscle lengthening) contractions tend to be more commonly identified. Examples would include squat thrusts, pushups, and biceps curls. Clarkson measured CPK in 203 healthy, but relatively physically inactive college students after 2 sets of elbow curls with weights for 25 repetitions. Mean CPK rose to a peak of 7713 at day 4, with a range of 50-80,550. The enzyme elevation lasted until day 10 post exercise. No participant developed any medical complications. ER has also been reported in a host of other physical activities including spinning, rock climbing, ice skating, and swimming. A common thread seen in ER is continued exertion beyond the point of fatigue. This is typically seen in a group setting, where peer pressure plays a role, or under the supervision of a demanding personal trainer.

RISK FACTORS
Asides from the type and duration of exercise, several other risks factors are associated with ER. Studies have shown that at baseline and post exercise, elevations in CPK are greater in men vs. women. Also CPK increments are greater in blacks vs. Caucasians. Increased muscle mass is thought to
explain the gender difference. The ethnic difference explanation is more elusive. One entertained mechanism is the prevalence of sickle cell trait, which may lead to an exaggerated raise in post exercise CPK. Another potential risk is any factor that may hamper bodily heat release. Drugs, particularly amphetamines, are implicated, as they cause peripheral vasoconstriction. Concordant with this hypothesis, is the fact that history of heat stroke may also be another predisposing factor. This was noted in a retrospective review by Hill in the military recruits. As a result, rubber suits, used by wrestlers to lose water weight have been banned. If ER is recurrent in an otherwise healthy, young patient, inherited muscle enzyme defects should be considered. The most common include carnitine palmitoyl transferase deficiency, myophosphorylase deficiency [McArdle’s disease] and adenosine monophosphate deaminase deficiency.

COMPLICATIONS

The serious complications of RM include ARF, hyperkalemia, DIC and compartment syndrome. Fortunately, these are all rare with ER. This is most likely due to the fact many of these patients are relatively young and healthy. If acute renal failure develops from ER, full renal recovery is nearly universal. Sinert® reported 35 ED admissions for ER with a mean CPK of 40,471. No patient developed acute kidney injury. Hill’s data reported an incidence of 8% in the 1203 cases of EH, all of whom recovered renal function.

One question frequently asked is, what level of CPK is associated with kidney injury? Although those who develop renal damage tend to have a higher CPK levels, the correlation between peak of CPK rise and acute renal failure is poor. Some studies have suggested renal injury is associated with CPK in excess of 20,000. However, there are also case reports of it occurring at 5,000. Complicating the issue is that there are frequently other contributing factors to renal damage in those studies. Meijer® reported the clinical course of 26 ICU admissions with severe RM, defined as CPK >10,000. The most common causes were ischemic and trauma, none due to exercise. Those who developed acute renal failure had a mean peak CPK of 55,366 vs. 28,643. However, there was substantial overlap between the 2 groups, and no defining level could be ascertained. Therefore, no CPK level has been established in the literature to predict ARF.

ARF from RM is the most serious complication that physicians are attuned to. It was first described in the medical literature in the 1940s by Beall and Bywater. They reported uremic deaths several days following crush injuries due to bombing raids in London. The mechanism of kidney injury is several-fold. Myoglobin, the heme-based oxygen carrying component in muscle is released into the circulation. It is believed to be toxic to the renal tubules. Secondly, there is a period of renal vasoconstriction hampering perfusion.

Lastly, there can be severe third spacing with fluid being sequestered into damaged muscle, leading to an effectively pre-renal condition. Due to the last mechanism, vigorous isotonic intravenous fluids have been the hallmark of preventive therapy. Volumes suggested range from 6-10 liters over the first 24 hours to maintain a urine output of 200-300ml/hour. The earlier the fluid administration, the better, a conclusion Ori Better® reported in crush victims from a collapsed building. However, therapy needs to be individualized, with close attention paid to the patient’s volume status. IVF administration to the point of overt fluid overload has been associated with increased mortality in ICU patients.

TREATMENT

The issue of type of intravenous fluid is still debated. Although urinary alkalinization can increase the solubility of myoglobin, the superiority of bicarbonate containing solutions over saline has not been confirmed. The same holds true for mannitol, another agent frequently employed to prevent and treat RM-associated ARF. In a retrospective review of 74 cases of kidney injury due to trauma-induced RM, Brown® found no benefit with mannitol or bicarbonate solution. In addition, there is a risk of osmotic induced tubular injury with mannitol administration. A serum osmolar gap >50 can predispose to this untoward complication.

Hypothetically, extracorporeal removal of myoglobin can be beneficial. Due to the size of the heme protein, it is not removed with conventional hemodialysis. However, plasmapheresis can effectively extract the compound from the vascular space. High flux continuous hemofiltration also can remove it as well. Regardless, there are no randomized studies that establish either modality as a preventative measure or treatment for ARF. Thus neither can be recommended.

SUMMARY

A post-exercise CPK rise is a common phenomenon. The defining line from a normal physiologic response to a disease state is a blurry one. When complications are initially apparent, then the distinction is obvious, but frequently, they are not present. Avoidance of alcohol, amphetamine-based drugs and the gradual increments in exercise intensity are recommended to attenuate ER. One issue is when to admit patients. Acute renal failure is quite rare and when it does occur, it almost always resolves completely. Therefore, in the absence of serious complications, the decision to admit is generally intuition based. CPK tends to peak at day 4, but can remain elevated for 1-2 weeks. If a patient presents without evidence of ARF, it would be unlikely to develop after generous IV isotonic fluid administration. Rate and volume of fluid needs to be individualized and clinically-based.
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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). 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.

Figure 1. a.) Intact ACL (asterisk), b.) Torn ACL (arrow)

ACL TEARS

Reconstruction of the ACL, while providing stability for daily activities and sports, does not prevent the later onset of PTOA, raising the issue of unrecognized injuries to articular cartilage and subchondral bone occurring at the time of injury and contributing to joint breakdown. Several studies have shown that coincident blunt impaction injury to articular cartilage and subchondral bone together with ACL disruption are associated with PTOA. 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 but 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.

**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
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. Non-contact ACL injuries include stopping mid-stride to respond to an opponent’s change in direction, especially in soccer, and an increase in loading 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. 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. 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). 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. This has been ascribed to increased valgus movements during landing, hormone levels, narrower intercondylar notch width, and smaller AC ligaments. Neuromuscular training programs suggest that enhancing body control may decrease ACL injuries in women. 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. 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. A stress magnitude of >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.

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. 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.

Table 1.

<table>
<thead>
<tr>
<th>Load</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>10MPa</td>
<td>No Chondrocyte Death</td>
</tr>
<tr>
<td>20MPa</td>
<td>No Chondrocyte Death</td>
</tr>
<tr>
<td>35MPa</td>
<td>50% Chondrocyte Death and Surface Fissures</td>
</tr>
<tr>
<td>50MPa</td>
<td>100% Chondrocyte Death and Gross Matrix Damage</td>
</tr>
</tbody>
</table>

**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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Predicting Success in ACL Reconstruction

ROBERT M. SHALVOY, MD

ABSTRACT
Anterior Cruciate Ligament (ACL) injury and ACL reconstruction is common in the United States. However, when compared to the standards of other orthopedics procedures today, ACL reconstruction is NOT predictably successful in restoring patients to their pre-injury state. Only 60–70% of reconstructed patients resume their previous level of activity and many patients experience some degree of osteoarthritis.

The reasons for such limitations of success are many. A recent renewal of interest in the many variables affecting ACL reconstruction and the understanding of the varying needs of patients with ACL injury holds promise for improving success even today as well as ultimately providing a normal knee for patients after ACL reconstruction.

KEYWORDS: anterior cruciate ligament reconstruction, knee kinematics, computer-assisted surgery

INTRODUCTION
ACL reconstruction is performed on 150,000 to 200,000 patients in the US yearly, a number that has been steadily growing for the past 25 years. Despite this popularity, the long-term outcome has been surprisingly disappointing with regards to restoring the anatomy, returning patients to their previous level of activity and maintaining a healthy joint, free from the symptoms of osteoarthritis. This is in part the result of a perception that ACL reconstruction is a routine surgical procedure for the general orthopedic community and supported by the fact that the majority of these reconstructions are performed by orthopedic surgeons performing less than 10 such procedures in a year. Additionally, after surgery the parameters of healing and rehabilitation needed to successfully return patients to pre-injury levels of function and performance remain poorly defined.

The problem lies in approaching ACL reconstruction as a routine, generic or “one size fits all” procedure. In this paradigm, graft failures have been reported as high as 25% in athletes under the age of 25, even in the best of hands. Likewise, the ability to return to previous levels of function among the most dedicated and elite athletes has been disappointing 60%. The solution is likely to lie in a better understanding of the injury and an individualization of the surgery to meet each patient’s needs. With the appropriate focus on the subtleties and variations of the ACL-injured knee, ACL reconstruction, rehabilitation and functional assessment, we can move towards recreating normalcy in the knee while at the same time indentify the limitations or short-comings of each reconstructed knee and reasonably predict success in terms of function and joint health. As we move in this direction, it is important that patients have a realistic expectation of ACL reconstruction and receive the appropriate counseling for making their best decision.

Knee Function and ACL Injury
The knee is one of the more complex joints in the body requiring great mobility and stability to function properly. This is accomplished in part by the various ligaments, both intra-articular and extrarticular. The ACL predominately controls against excessive anterior movement or translation of the tibia along with internal rotation of the tibia with respect to the femur and the rest of the body above it. The ACL is a major stabilizer of the knee in pivoting activities and in positions of knee flexion ranging from 15–30 degrees. This range comprises the majority of athletic functions as well as many activities of work and daily living. Given the ACL’s limited blood supply and the effects of the synovial fluid environment that surrounds it, torn ACLs have no ability to heal after injury leading to altered mechanical function in the knee. It is important to note that the knee joint has a variable if not unique balance of mobility that suits one’s own neuromuscular system of control resulting in a likewise unique functional starting point. The ACL injury alters knee function at this balance point creating a new “pathologic” balance point. The effect on function can vary from minimal effect to greatly disabling. To further complicate this picture, the ACL is rarely injured in a vacuum, meaning that even without frank tearing of other ligaments or the menisci, the surrounding soft tissue structures can be strained or stretched in a variety of patterns corresponding to the forces of injury that further alter the stability in both subtle and overt ways that leads to what is arguably a unique instability from ACL injury.

Recent work using computer navigation technology to measure knee kinematics during ACL reconstruction has confirmed variable patterns and magnitudes of instability resulting from what has been considered an “isolated ACL tear.” Clearly, a mindset of treating a variable pattern of
injury with a fixed solution paradigm is likely to successfully address only some patterns of injury while allowing others to fall through the cracks due to this variability and result in a limited correction or incompletely addressed pathology. This incomplete correction can itself result in poor function of the knee as well as allow abnormal stresses on the joint contributing to the eventual failure of the components that were corrected such as the ACL. [Figures 1 and 2]

**Figure 1.** Left knee with optical trackers applied for computer-assisted ACL reconstruction

**Acute Care**

From the patient’s perspective, an ACL tear is a situation of acute pain, swelling and stiffness. The concept of instability is not always perceived or understood at the time of injury as the core of the problem. Knowing that surgery is typically prescribed and wanting to return to sports as quickly as possible, most athletes, young and not so young, proceed with surgical reconstruction before the acute phase resolves. When that happens, the patient goes without pre-surgical rehabilitation that can define for the patient his or her true impairment as well as allow time to address the neuromuscular and psychological components of the injury that can impact the ultimate outcome of surgery. Our own work has shown that these psychological elements have as much impact ultimately on function – positively or negatively – as knee kinematics. Therefore, it is important that this is addressed prior to surgery.

**ACL Reconstruction**

Only once the exact pattern of instability has been identified and the distinct needs of the patient thoroughly addressed can ACL reconstruction be successfully performed with confidence. With this knowledge, the variables can be customized to address the needs of the patient. These variables include the timing of surgery (including the decision for nonoperative treatment), the type of graft material used, the number of grafts, graft fixation and additional extra-articular surgery when necessary. No single surgical technique can address all needs or situations successfully. With the use of intraoperative computer navigation, the direct effects of surgery on knee kinematics can be immediately assessed during surgery and the course of surgery modified to attain the desired outcome. Referred to as “on demand” ACL reconstruction, the result is a customized reconstruction with immediate documentation of the reestablished kinematics of the knee. [Figure 3] The expectation is that this will result in a better functioning knee and a greater likelihood of returning to previous functional activities.

**Figure 2.** Computer graphics obtained during computer-assisted ACL reconstruction. Image documents precise tunnel placement in reference to intra-articular landmarks.

**Figure 3.** Knee kinematics obtained immediately after ligament fixation using computer navigation
Post-op Healing and Rehabilitation

After surgery, a healing process is required for the grafted tendon material to remodel into a viable, dynamic ligament. While the acute phase requires 12 weeks, healing, complete or otherwise, is not guaranteed. Furthermore, no known graft tissue has the unique structure and mechanical function of the native ACL. The goal of surgery is to anatomically restore the ligament tissue in the best possible way and through remodeling attain the best functional equivalent. While the nuances of surgery as previously described can greatly affect this, establishing a nurturing intra-articular environment post operatively is equally important. Physical therapy is an important adjuvant that can help create such an environment.

Physical therapy is used to restore range of motion, reduce swelling and restore neuromuscular function. When done appropriately, this stimulates articular cartilage, helps normalize the synovial fluid environment and provides a positive stimulus for the healing ACL graft. Under stimulating or over stimulating the knee is thought to adversely affect graft healing and therefore knee function. ACL rehabilitation is a subspecialty of physical therapy requiring close supervision and on-going feedback between patient, therapist and surgeon.

Function

While biological healing largely occurs during the first 12 weeks following surgery, no good determination of restored function exists. While validated research instruments exist, these have been patient-reported outcomes and not true functional assessments. Single-leg hop and triple-hop testing through physical therapy have provided simple estimates of function but the need for better tools and methods of assessment is reflected in the alarmingly high incidence of reinjury in select groups of athletes returning to sport 6 or 7 months after surgery. Similarly, the high incidence of injury to the contralateral ACL upon returning to sports implies an incomplete restoration of function in the recovering ACL patient.

CONCLUSION

ACL injuries are common. They frequently have a devastating impact on knee function and can ultimately lead to joint degeneration. The traditional assumption has been that surgically restoring ligament anatomy will result in restored joint kinematics and thus joint function. Short- and long-term outcomes research has failed to identify the limitations of current practice. As Lord Kelvin stated over a century ago, "if it cannot be measured, it cannot be improved." Currently available technologies, such as computer navigation, can be part of an increased effort to better assess and therefore better correct the pathology of ACL injury and ultimately measure the effect of surgical reconstruction on functional outcome. Patient selection, detailed, individualized surgical planning, in-depth patient education, precise intra-operative joint assessment and ligament reconstruction are all necessary now and are more likely to predict success in ACL reconstruction.

References


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