

Anterior Cruciate Ligament Injury: Current Understanding of Risk Factors

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Abstract

Reconstruction of the anterior cruciate ligament (ACL) is a common surgical procedure with an estimated 50,000 procedures in the US annually. Injury of the ACL often requires costly treatment, extensive rehabilitation, and results in early osteoarthritis. While ACL ruptures occur secondary to a complex interplay of multiple variables, a number of risk factors have been identified that increase risk of ACL rupture. We will analyze a variety of identified risk factors including anatomic, neuromuscular control, hormonal, genetic, and external variables.

In terms of intrinsic risk factors, multiple recent studies have identified neuromuscular risk factors that put the ACL at risk for injury. These studies show differences in neuromuscular control of knee joint mechanics, hamstring muscle strength and core stability in patients who sustain ACL injury.

Anatomical variants between individuals, genders and races have also been implicated as risk factors for ACL injury. These risk factors include femoral intercondylar notch width, tibial slope geometry, ACL dimensions, and generalized ligamentous laxity. Studies have sought to evaluate the interactions between absolute femoral notch width, notch width index, and intercondylar notch shape and how these factors relate to ACL injury risk. Postulating that an increased anteriorly directed shear force on the tibia correlates with higher incidence of ACL injury, studies have identified an increased posteriorly directed tibial slope and shallow medial depth of the tibial plateau, as significant risk factors for ACL injury. Newer research suggests that meniscal geometry factors into this equation as well. Other studies have suggested that decreased ACL volume is a contributing factor, while further studies propose that ACL injury risk can be predicted as a factor of generalized joint laxity. Lastly, prior ACL injury and reconstruction have been implicated as risk factors for future knee injury. Patients undergoing ACL reconstruction are at higher risk for contralateral ACL injury and ACL rerupture postreconstruction compared to individuals without prior ACL injury.

Additionally, hormonal and genetic factors have been connected to ACL injury. After estrogen and progesterone

receptor sites were found on the ACL, multiple studies have analyzed hormone levels and ACL rupture risk. Overall, the results of these studies are varied and controversial, but suggest an increased risk in the preovulatory menstrual cycle phase. Genetic studies have shown specific mutations that place patients at risk for ACL injury and other tendon injury. Also, a study has shown that patients with an ACL rupture were more than 4 times as likely to have a relative with history of ligament injury.

External variables for ACL injury include cleat design, drier weather conditions and certain playing surfaces, that have been shown to contribute to increased incidence of ACL injuries.

Neuromuscular Control

Anterior cruciate ligament loading and failure is a well studied phenomenon with numerous cadaveric models, computer models, and observational studies aiding our understanding. The majority of ACL injuries are due to non-contact mechanisms. Video analysis of ACL injuries show most of these injuries occur with knee extension during a deceleration or landing maneuver [1]. Other analyses have shown lateral trunk motion and posterior weight distribution as other risk factors for ACL injury. These observations are confirmed by cadaveric studies showing high ACL strain with the coupling of knee rotation, tibial compression, and knee abduction [2-4].

Given that ACL injuries appear to occur following a common mechanism further studies have analyzed neuromuscular control to see if individuals at risk for injury can be identified, if neuromuscular control may explain the sex based differences in ACL injury and if neuromuscular training can be used to reduce at risk motions and ultimately ACL injury.

A number of motions have been assessed to predict ACL injury. [5] and Hewett et al have shown lateral trunk motion as an independent risk factor, but only in female athletes [5-7]. Valgus collapse of the knee has been identified as a risk factor in both male and female athletes [8,9]. However, female athletes appear to land with more knee and hip flexion as well as considerably more valgus collapse than male players [9]. An electromyography study further supported these sex related

differences showing decreased knee flexion, hip flexion, hip abduction, and increased quadriceps activation during landing in female subjects [10]. These landing characteristics may be partially explaining the increased rate of ACL rupture in females.

To predict ACL rupture, the Landing Error Scoring System (LESS) has been developed. The LESS uses a scoring system based on jump landing biomechanics to identify athletes at risk for lower extremity injury. In youth soccer players the system has been shown to predict noncontact injury [11,12]. However, the LESS has not predicted injury in all studies [13] and will require future research to determine its predictive capacity across all age groups.

Lastly, preventative training exercises have been developed to reduce neuromuscular factors contributing to ACL injury. These exercises appear to reduce ACL injury rates in females, but require a considerable time commitment (23 times/week) [14-18]. Further research is needed to determine their protective ability in male athletes.

ACL Dimensions

Inferences that smaller sized ACLs correlate with greater likelihood of noncontact injury have led researchers to investigate the ligament's overall dimensions and its effect on injury rates. Several studies have evaluated, using MRI analysis, the contralateral ACL of patients with noncontact ACL injuries and compared it to a group of matched controls. Using MRI based volume calculations, one study demonstrated a significantly decreased ACL volume in the injured population compared to the control group [19]. Another study yielded similar findings that were limited exclusively to the male group, suggesting variations in the anatomic features that predispose each gender to injury [20].

Femoral Intercondylar Notch Geometry

The intercondylar notch of the femur houses a portion of the ACL, and from as early as 1936, it has been speculated that injury to the ligament results, in part, from entrapment of the ACL at the notch during the course of specific motions. Researchers have studied the interplay between several variables related to femoral notch dimensions and identified characteristics that place an individual at increased risk for sustaining a noncontact ACL injury.

Femoral notch width is a well studied anatomic feature that has shown to be variable across genders and races, and may offer a partial explanation for differences in ACL injury rates between the groups [21]. Although conflicting studies exist, recent meta-analyses reveal that smaller notch widths, on average 2.15 mm or less, are correlated with increased rates of ACL injury. It has been suggested that stenotic intercondylar notches increase the vulnerability of the ACL to stretching over the medial border lateral femoral condyle particularly during valgus loading of the knee [22].

Notch width index (NWI) is a more specific measurement with similar implications for ACL injury. Initially described by Souryal, NWI is defined as the ratio of the width of the intercondylar notch at the level of the popliteal groove, to the femoral bicondylar width taken at the same level [23]. His initial

study implicated a decreased NWI as a risk factor for bilateral ACL injuries when compared to matched controls. A subsequent study defined notch stenosis as NWI less than 0.20 mm, and identified it as a threshold for increased injury risk. Multiple studies have evaluated similar variables, and come up with different definitions of notch stenosis. Although several trials have not found similar correlations, [22] performed a meta-analysis evaluating 16 studies, concluding that such a correlation exists [22].

More recently, variations in notch morphology have been identified as potential sources for ACL impingement and injury. Using MRI analysis, [24] evaluated three potential shapes of femoral intercondylar notches, and retrospectively evaluated the risks of ACL injury for each, as well as for NWI [24]. Type A notches are defined as narrow from base to apex, Type U notches do not narrow past the midsection, and Type W notches are similar to U's but with a bifid apex. The study showed a significant association between A shaped notches and ACL injury, and found no association between smaller NWI and injury.

Tibial Plateau Geometry

The geometry of the tibial plateau, specifically the depth and slope, is a more recently discovered risk factor with significant implications on ACL injury. As the tibial plateau is a complex geometrical surface, with numerous variables factoring into its motion, studies have sought to model and identify which features have the greatest impact on noncontact ACL injuries. In the most essential sense, the posterior tibial slope describes the angle between a line tangential to the tibial plateau surface, in the anterior-posterior direction, and a line perpendicular to the lengthwise axis of the tibia. Averages have been reported as $10^{\circ} \pm 3^{\circ}$, with deviations altering the kinematics of the swing and stance phases of the knee joint [25]. Using MRI analysis [26], identified increased posterior inferior directed tibial slopes and shallow medial tibial plateau depth as an anatomic variant found more commonly in the ACL injured population [27]. Further, they began to identify differences in risk factors for each gender, which will be highlighted in a later section.

Additional studies have corroborated these findings and expanded on the postulated mechanisms for this risk [28,29]. Cadaveric studies have demonstrated that artificially created increases in the tibial slope correlate with increased anterior translation forces on the tibia relative to the femur [30]. As the ACL is the primary restraint to such forces, it is believed that increased strain is experienced with such anatomic variants in vivo. The depth of the tibial plateau has been thought of as a general indicator of motion constraint across the joint, and a shallow medial plateau surface has been suggested to contribute to an increase in the internal rotation forces experienced by the tibia during compressive loading.

These forces have been shown to be a product of the tibial bony surface as well as the overlying articular cartilage, and surrounding tissues [31]. It is important to recognize that following ACL injury, the articular cartilage of the tibial plateau has been demonstrated to undergo morphologic changes, specifically flattening in the medial compartment and increased posterior sloping in the lateral compartment, when compared to the contralateral knee. As such, the majority of studies analyze

the geometry of the uninjured knee when evaluating articular morphology. Beynon et al. analyzed the cartilaginous profile of the ACL injured population compared to a matched uninjured cohort and found that similarly, an increased posteriorinferior slope along the lengthwise axis of the tibial plateau was associated with an increased risk for ACL injury [32]. Several studies have even implicated variations in meniscal geometry as potential risk factors for ACL injury. A similar effect of increased anterior tibial translation has been demonstrated in individuals with increased lateral meniscal slopes, which was previously shown to correlate with increased ACL injury.

Body Mass Index

Perhaps the only modifiable risk factor, the role of body mass index (BMI) has been evaluated with regards to non-contact ACL injury. In two studies evaluating ACL injury in military populations, BMI was shown to be a risk factor, although not universally. A retrospective evaluation of 2,345 U.S. Naval Academy midshipmen suggested that a BMI 1 standard deviation above the gender specific mean, in conjunction with a decreased femoral notch width, was a significant risk factor for ACL injury in both genders, while independently neither notch width nor BMI was significant [33]. A similar study evaluating cadets from the United States Military Academy found that BMI was a significant independent risk factor in females, but not males [34]. Comparably, this effect was amplified when combined with a narrow femoral notch width. Although the reasoning isn't as straightforward, BMI's influence on ACL injury can play an important role identifying at risk individuals and starting possible interventions.

Ligamentous laxity

Ligamentous laxity, both generalized and kneespecific, has been explored as a potential risk factor for ACL injury. The Beighton hypermobility score is a ninepoint scale used to assess generalized joint laxity and ligamentous hypermobility. Several studies have examined the relationship between increased Beighton scores and ACL injury rates, and identified generalized joint laxity as a risk factor for ACL injury in both male and female populations [35,36]. Knee specific laxity measurements, evaluated using a KT1000 arthrometer, or goniometer for the presence of genu recurvatum, have yielded similar associations for ACL injury [34,36]. As females have been shown to have greater amounts of knee and generalized joint laxity, these findings may offer partial explanation as to why the overall incidence of ACL injury is greater in the female gender.

Composite/Gender Variability

It is important to recognize that significant variability exists between male and female knee morphology, even when controlling for disparities in height and weight. Features such as narrower femoral notch widths, increased posteriorinferior tibial plateau slopes and decreased ACL width have been shown to more prevalent in the female population than in their male counterparts [27,37]. As such, overall rates and specific combinations of anatomical variants have been shown to differ between the genders.

In an MRI analysis of firsttime, noncontact ACL injuries in both

male and female participants, compared to a sample of uninjured matched controls, [20]. identified differing combinations of knee joint geometry that put members of each gender at increased risk for injury. While males with smaller ACL volumes, medial tibial spines, and decreased lateral compartment posterior meniscal angles were at a significantly higher risk for injury, the best fitting model of injury for females included decreased femoral notch width and increased posteriorinferior directed lateral compartment tibial cartilaginous slopes [20]. Although these findings may seemingly muddle an already complicated issue, they serve to highlight the important fact that combinations of features, rather than individual morphological differences, are the most likely explanation for variable susceptibility to ACL injury between individuals.

Prior ACL Injury or Reconstruction

Individuals who have undergone ACL reconstruction previously have been shown to be at an increased risk for graft reinjury and contralateral knee injury. In one study evaluating professional Swedish soccer players, a prior ACL injury was identified as a significant risk factor for sustaining a new knee injury of any kind. This risk did not extend to other lower extremity injuries or total body injuries [38]. Interestingly another study found a significant correlation between prior ACL reconstruction and increased risk of ipsilateral ankle injury. In an Australian study evaluating football players, [39]. found that prior ACL reconstruction put a player at a significantly increased risk for both ipsilateral and contralateral knee injury, with the effects being most prominent in the first 12 months following injury (12.3 times more likely) but still significant for ACL injuries sustained greater than 12 months prior (4.4 times more likely) [39]. It has been suggested that scar tissue, decreased range of motion and alterations in proprioception may provide explanation for these trends.

Hormonal Risk Factors

Sex hormones have been postulated to play a role in ACL pathogenesis after hormone receptors for estrogen, testosterone, relaxin and progesterone were localized to the ACL. It is known that female athletes have a two to eightfold greater incidence of ACL injury compared to male athletes [41-43]. This increased female incidence is likely a result of multiple sex related factors including anatomic, strength, and laxity differences. However, sex hormones may also play a role. Supporting this hypothesis, multiple hormone receptors have been identified on the ACL and there also appear to be sexrelated differences in expression of these receptors.

Relaxin is a peptide hormone found in the serum of both pregnant and nonpregnant females thought to be responsible for connective tissue remodeling during pregnancy [44]. It is known to have collagenolytic effects secondary to MMP release [45,46]. Relaxin receptors have been identified on the ACL and with their potential collagenolytic effects have been proposed as a potential risk factor for rupture [47]. Animal models show increased laxity and strength in pregnant females with ACLs [48]. Dragoo et al analyzed ACL sections from both men and women with ACL ruptures for relaxin receptors. This is further supported by [49]. who found higher rates of relaxin binding in injured female ACL specimens. However, she did find relaxin

binding in 1/3 of the male ACL specimens [49]. Dragoo et al. [50] also elevated levels of relaxin in female NCAA athletes with ACL injury versus noninjured controls [50]. Given these findings, he concluded relaxin may play a role in ACL rupture in females.

Relaxin expression is believed to be regulated by estrogen as there appears to be upregulation of relaxin receptors after pretreatment with estrogen in animal models [51]. Estrogen itself may also play a role in ACL pathogenesis. Liu et al. [52] identified progesterone and estrogen receptors on synoviocytes, fibroblasts, and blood cells of injured ACLs in both females and males [52]. In a rabbit animal model, ACL strength decreased after exposure to pregnancy levels of estrogen [53]. In a rodent model, human relaxin caused decreased collagen accumulation [54] and in another caused changes to collagen structure [27]. Sciore et al. [55] localized estrogen and progesterone receptors to the ACL and via reverse transcription-polymerase chain reaction showed differences in expression after sex hormone binding between sexes [55]. However, estrogen effects on ACL fibroblasts has been studied in vitro with varying results: Yu et al. [56] found inhibition of collagen synthesis with estrogen while Seneviratne et al. [57] found no direct effect on ACL fibroblasts [57,58].

Given these findings that estrogen may participate in ACL pathogenesis, research into the effect of these hormones throughout the menstrual cycle was undertaken. The effects of the menstrual cycle on the ACL remain controversial. The menstrual cycle has varying stages of hormone release with a gradual increase in estrogen during the follicular phase followed by a relative decrease in estrogen production and increased progesterone until the late phase of the luteal phase. Across the menstrual cycle, Shultz et al. [59] has shown alterations in knee joint laxity as well as changes in serum collagen breakdown and production markers [59]. However, Karageanes et al. [60] followed female high school athletes over an 8 week period using questionnaires to report menstrual phase and an arthrometer to measure laxity and found no variation in ACL laxity throughout the menstrual cycle [60].

If there is a higher risk phase of the menstrual cycle, the exact phase remains controversial. Myklebust et al. [61] carried out a prospective study on female handball players and found a higher incidence of ACL injury in the late luteal phase [61]. However, the majority of studies suggest the preovulatory phase is the highest risk phase [62-66]. Only two of the six referenced studies measured hormone levels as the other four studies relied on questionnaires for determination of menstrual phase. Further controversy exists regarding the relationship oral contraceptives have on ACL injury with Arendt et al showing a significant relationship and Ruedi et al. [64] showing no increased risk of injury with oral contraceptive use [64,65]. Additional studies are needed in to more precisely determine the exact role of each hormone and determine how these hormones exert their effects throughout the menstrual cycle.

Genetic Risk Factors

Genetic risk factors for ACL rupture remains an area of ongoing study. Two research groups have shown familial predisposition toward ACL rupture. Harner et al. [67] carried

out a matched casecontrol study and found patients with ACL tears had a significant difference in family history of ACL rupture [67]. This was further supported by a matched casecontrol study analyzing familial predisposition toward ACL rupture. Matching was based on age, gender, and primary sport. They found patients with an ACL tear were over 2 times as likely to have another family member with an ACL tear. Posthumus et al. [68] found a similar family association with ACL rupture [68].

Differences in gene expression also may explain the increased incidence of ACL pathogenesis in females. Johnson et al have shown upregulation of aggrecan (important extracellular matrix component) and fibromodulin (controls collagen fibril synthesis) and downregulation of WNT1 inducible signaling pathway protein 2 (regulates collagen homeostasis) in females with injured ACLs versus males [69].

At this point there are a number of casecontrol studies showing association between specific gene variants and ACL rupture. Many of these studies focus on collagen related genes as Type I collagen comprises 70-80% of dry ligament weight [70]. Some of these genes also appear to confer increased risk of Achilles tendinopathy and rupture. Khoschnau et al. [71] analyzed type 1 collagen polymorphisms in a matched case control study. Specifically, they studied single gene polymorphisms in the promoter region of COL1A1 (a regulator of type 1 collagen production). They found significant decrease in ACL rupture risk and shoulder dislocations in patients with certain polymorphisms [71]. This was followed with a number of case control studies by a South African research group lead by Michael Posthumus, to look at other collagen related genes. Notably, this research group has included only Caucasian participants. In 2009, Posthumus et al. [72] analyzed the COL1A1 gene, but this time used gender matched controls as opposed to Khoschnau who used female controls with both female and males in the injury group. Posthumus et al [72] found a rare TT genotype of COL1A1 that was significantly underrepresented in participants with ACL ruptures suggesting it was protective against rupture [72]. Posthumus et al. [72] carried out a similar study analyzing COL5A1 in female athletes and found a specific CC genotype that was significantly underrepresented in participants with ACL rupture again suggesting a possible protective role for that genotype [72]. Further study turned to COL12A1 which encodes for type XII collagen believed to regulate collagen fibril diameter [73]. Posthumus et al. [74] showed an association between a specific COL12A1 AA genotype and ACL rupture in females [74]. Four matrix metalloproteinases (MMPs) on chromosome 11q22 have also been analyzed. These MMPs are responsible for extracellular matrix degradation and remodeling and therefore play an important role in ligament homeostasis. Posthumus et al. [75] found that AG and GG genotypes of MMP12 were significantly underrepresented suggesting a possible protective role conferred by these genotypes [75]. Growth factors like MMPs also play a role in ligament homeostasis. A variant of growth differentiation factor 5 (GDF5) is known to stimulate production of type 1 collagen in rabbit ACL models [76]. Given these findings, it was hypothesized that the GDF5 rs143383 variant would provide a possible protective effect for ACL rupture. However, Raleigh et al. showed in a matched casecontrol with Caucasian males and females there were no association

between the GDF5 rs143383 variant and ACL rupture. Lastly, the most recently published research in genetics and ACL pathology reports an association with a specific GG genotype of fibrillin2 (FBN2) and ACL rupture in a casecontrol study [77]. Fibrillins are glycoproteins present in the extracellular matrix of ligaments and tendons [78]. Fibrillin 2 specifically plays a role in the composition of elastic fibers [79].

As you can see, genetics appears to play an important role in ACL pathology. The number of genetic associations will likely continue to grow and more diverse populations will go under study.

Extrinsic Risk Factors

Extrinsic risk factors for ACL injury include weather conditions, footwear and playing surface. These are not inherent to the individual and therefore offer a more modifiable risk source. As modern day athletics see continued innovations in equipment and arena alike, studies evaluating these extrinsic factors may serve as a viable foundation for future interventions.

Weather

Weather conditions have been extensively studied in regard to ACL injury incidence. As professional sports feature performance athletes playing in highly documented conditions, they offer ample material for risk factor analysis.

The National Football League is one such organization, and several studies have evaluated the relationship between weather conditions and ACL injuries in the league. In one study analyzing a total of 5910 NFL games over 10 seasons, the author's identified significantly higher rates of ACL injury in earlier parts of the season, associated with warmer weather conditions, in comparison to later/cooler parts of the season, on both artificial and grass playing surfaces [80]. Unsurprisingly, this trend was no longer significant when artificial climates, such as dome stadiums, were analyzed. It is postulated that decreased amounts of shoesurface traction in cooler months are one component of this increased risk.

Specifically regarding climate, Walden et al. evaluated regional differences between ACL injury rates in European professional soccer players. Dividing teams into groups using a standardized climate classification system, the researchers found that noncontact ACL injury rates were significantly less in northern regions, an area associated with cooler winters and the absence of a dry season. Interestingly, the opposite trend was found for upper body, low back and Achilles tendinopathy injuries [81].

Orchard et al published multiple studies evaluating the risk factors for ACL injury in Australian footballers. One study identified drier playing conditions: high water evaporation in the previous month, and low rainfall the prior year, as significant risk factors for player ACL injury [40]. In an attempt to provide a direct correlation between ground hardness and ACL injury rates, Orchard used readings from a penetrometer, a device that measures surface hardness, and compared them to incidence of ACL injury in AFL players [41]. Although no significant findings were made, there was a trend supporting prior studies' results that matches in earlier months/warmer conditions play some

part in ACL injury risk.

Footwear

Few studies have evaluated the relationship between footwear and ACL injury risk. In one prospective study, 3,119 high school level American football players were followed for 3 seasons and the incidence of ACL injury was measured, as well as their playing footwear. It was found that edge design cleats, those with longer cleats around the shoe's periphery with shorter inner cleats, produced higher amounts of torsional resistance and were associated with significantly increased ACL injury rates when compared to pivot disk, flat, and screw in designs [82]. Another study found that shoesurface interactions vary with the ambient temperature, and increased force is required to release a shoe from an artificial turf surface at higher temperatures than lower temperatures, a finding that may provide mechanism to previously mentioned correlations [83].

Turf

Playing surface represents an easily modifiable risk factor for athletic teams that has unfortunately yielded mixed findings. Numerous studies have been conducted to evaluate the difference between artificial surfaces and grass regarding ACL injury risk. While several studies have suggested have argued that there is a significant difference between artificial and natural surfaces [83,84], multiple others suggest that no significant difference exists [80,86,87]. It is difficult to speculate on the nature behind these mixed findings, but further analysis needs to be done if a clear trend is to be discovered.

Interestingly, amongst different types of grass, variations in ACL injury rates have been found. Orchard et al. [88] evaluated 4 different types of natural grass playing surfaces on Australian Football fields and identified that Rye grass was associated with significantly decreased rate of ACL injury when compared to Bermuda grass. The authors speculate that this may be a result of the thick thatch layer found in Bermuda grass, that likely increases gripping between cleats and the playing surface [88].

Discussion

Anterior cruciate ligament rupture is an injury that often results in costly treatment, extensive recovery and numerous immediate and longterm complications. The risk of ACL injury is a complex interplay of factors both intrinsic to the individual and extrinsic to the activity or playing conditions. Although individual risk factors have been identified further research is needed to determine the mechanics of ACL injury in all population groups, the interplay between risk factors, and ultimately further prevention of these injuries.

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