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Review Article

Gender Differences in Anterior Cruciate Ligament Injury: A Review of Risk Factors, Mechanisms, and Mitigation Strategies in the Female Athlete

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Abstract

Anterior cruciate ligament (ACL) failure or rupture is a common orthopedic injury that occurs when an athlete applies a force that exceeds the ACL's failure load and is typically generated through a variety of mechanisms including anterior shear force, axial compressive loads in knee hyperextension, and internal tibial rotation. Incidence rates of ACL injury are estimated to be 2.4-9.5 times greater in females than males and most commonly occur in sports that require athletes to pivot and rapidly change direction as well as those that require jumping and landing maneuvers. Current literature suggests that the increased risk for ACL injury in females is multifactorial and influenced by a combination of anatomical and hormonal factors more predominant in females versus males. Possible anatomical factors associated with an increased risk of ACL rupture in females include narrower femoral intercondylar notch widths, wider pelvic widths, increased Q angles, lower hamstring to quadriceps ratios, and differences in knee and hip range of motion and laxity, although whether these factors are truly contributory is currently debated. Additionally, fluctuations in hormones such as estrogen and relaxin throughout the menstrual cycle are thought to contribute to biomechanical changes in the ACL that predispose women to ACL rupture. Various injury prevention programs for female athletes have been identified, the most prominent of which is neuromuscular training, and however heterogeneity in program design precludes the ability to provide definitive clinical recommendations and highlights an area for future higher quality comparative studies to better guide optimal injury prevention program design.

Key Words: anterior cruciate ligament; ACL; female athletes; sex differences in ACL Injury; hormonal factors to ACL injuries; ACL injury prevention; female athlete triad

Introduction

Composed of a complex combination of parallel, helical, and nonlinear collagen fibers, the anterior cruciate ligament is a key stabilizer of the knee joint.[1, 2] Though variations can exist, it is commonly accepted that the ACL is composed of two bundles: the anteromedial bundle (AM) and the posterolateral bundle (PL).[3-6]. During knee extension, the PL bundle becomes taut and the AM bundle is more lax; this relationship is reversed during flexion.[6, 7] Together, these bundles enable the ACL to prevent anterior tibial translation, but more recent studies have also provided a biomechanical argument for the ACL's role in the rotational stability of the knee joint.[6-9]

ACL failure or rupture is a common orthopedic injury that occurs when an athlete applies a force on the ligament that exceeds its failure load.[10] These injuries can be devastating due to their high healthcare utilization costs, long rehabilitation process, and associated long-term complications such as osteoarthritis and arthrofibrosis of knee joint [11-13]. Injurious forces can be generated through a variety of different mechanisms such as anterior shear force, axial compressive loads, hyperextension, and internal tibial rotation [12, 14]. It was recently estimated that the annual adjusted incidence of ACL tears was 68.6 per 100,000 person-years.[15] Peak incidence rates for males occurred between the ages of 19 and 25 (241 per 100,000 person-year) and for females, between the ages of 14 to 18 (227.6 per 100,000 person-years) [15]. Injury rates vary across different sports. A 9-year review of NCAA injury data by Agel et al. demonstrated that the highest annual rates of ACL injury in men occurs in football (.17 per 1,000 athlete exposures) followed by wrestling (.15 per 1,000 athlete exposures) and lacrosse (.13 per 1,000 athlete exposures).[16] The highest annual rates of ACL injury in women were found in gymnastics (.24 per 1,000 athlete exposures), lacrosse (.23 per 1,000 athlete exposures), and basketball (.22 per 1,000 athlete exposures).[16]

ACL reconstruction is considered the gold standard for restoring knee stability and functionality after injury [17-20]. The success of ACL reconstruction can be measured by the post-operative return to sport (RTS) rates, which can often vary depending on the reconstruction type and patient population. A study by Lai et al. reported an 83% RTS rate for elite athletes undergoing ACL reconstruction.[21] Rates of return to a low level of play can be even higher, with one study reporting rates as high as 91.9% of patients to resuming recreational play [22]. However, rates of return to pre-injury level after ACL reconstruction have been less promising, estimated to be between 48.5%-63% emphasizing the need for further research on maximizing patient outcomes [23-26].

Incidence rates of ACL injury are estimated to be 2.4-9.5 times greater in females than males, and most commonly occur in sports that require female athletes to pivot and rapidly change direction as well as those that require jumping and landing maneuvers [27-31]. A study by Shi et al. explored the occurrence of ACL injuries in male and female alpine skiers and noted a greater prevalence of ACL injuries in female skiers even though rates of vigorous activity were reported to be lower in females versus males. These results suggest the observed differences in incidence rates of ACL injuries between the sexes is less likely due to the intensity of the physical endeavor performed and suggests the existence of inherent factors that increase the risk of ACL injuries in females. [32] In current literature, multiple explanations for this discrepancy in incidence rates have been proposed including differences in lower extremity anatomy and hormonal fluctuations. This review will explore variables contributing to a higher incidence of ACL injuries in female athletes, summarize proposed mechanisms that increase risk of injury, and provide insight to potential risk mitigation strategies for preventing ACL injury in female athletes.

Anatomical Differences between Sexes contributing to ACL Injury

Intercondylar Notch Width, Pelvic Width, and Q Angle

Anatomical differences between males and females are often cited in literature as predisposing factors for ACL injury in females. A prospective study by Shelbourne et al. of 714 patients with ACL tears explored the relationship between the width of the femoral intercondylar notch, as measured radiographically, and incidence of ACL re-injury.[33] Although no significant differences were found between males and females in this cohort in terms of reinjury rate, the authors noted a significantly narrower femoral intercondylar notch in females versus males.[33] Previous systematic reviews have shown that a wider intercondylar notch was protective in terms of sustaining an ACL injury, with narrower intercondylar notches associated with increased likelihood of injury [34, 35]. Other authors have proposed that a narrower notch increases the likelihood for impingement of the ACL between the femoral condyle and the tibial plateau, particularly in maneuvers that require twisting and pivoting of the knee.[29, 36, 37] In addition to intercondylar notch width, other studies have inferred that the risk of ACL injury is positively correlated with pelvic width and Quadriceps (Q) angle.[30, 33] However, these results have conflicted with a prospective case-control study by Mohamed et al. in female soccer players that demonstrated no significant differences in ACL tear rates based on Q angle, pelvic width, and intercondylar notch width [38].Although it is important to note that the sample size was relatively limited and potentially may have been underpowered in detecting a significant difference.[38] Whether such metrics directly contribute to ACL injury remains controversial and presents the opportunity for future studies to explore the strength of this association.

Hamstring – Quadriceps Ratio

The hamstring - quadriceps (H/Q) ratio provides a metric for assessing the two main opposing forces (flexion and extension) of the knee joint and allows for an estimation of muscle balance in the lower extremities [39, 40]. Lower H/Q ratios indicate a dominance of the extensor and weakness of flexor mechanisms and highlights a predisposition to produce strain on the ACL during moments with anterior translation of the tibia and precludes knee joint stabilization by the flexor mechanism.[30, 39, 41] Relatively low H/Q ratios have been characterized in women versus men, thereby indicating a potential mechanism for increased risk of ACL injury in this group.[36, 42] Additionally, this presents an avenue for patient counseling and risk mitigation strategies via correction of lower extremity muscle imbalance and hamstring strength training in female athletes involved in high-risk sports [43].

Differences in Hip and Knee Range of Motion and Ligament Laxity

Differences between range of motion (ROM) in the hip and knee joints in females has been suggested in literature as a potential reason for increased risk of ACL injury. Previous studies have shown that females have a greater ROM in internal and external hip rotation than males due to greater ligamentous laxity [29, 44, 45] .The greater ROM of the hip in females can potentiate the risk of noncontact ACL injuries through creating large dynamic knee valgus moments that are believed to be contributory to ACL injury [29, 45, 46]. Additionally, increased range of motion of tibial external rotation and abduction in females can create a predisposition for ACL impingement on the lateral wall of the intercondylar femoral notch[29] .

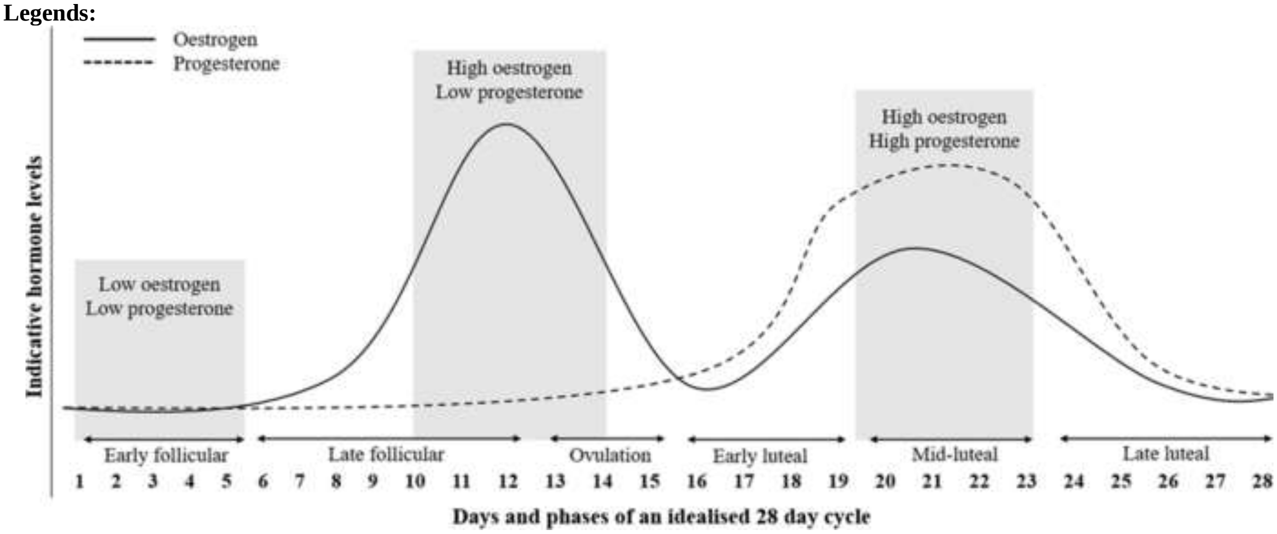
Hormonal Influences on Risk of ACL Injury

Estrogen

Fluctuations in serum estrogen are thought to play a major role in increasing ACL laxity, and thereby creating a predisposition for injury [47]. Estrogen has been implicated in altering ACL ligament laxity and collagen support of the ligament [44, 47] .A study by Liu et al. utilized a rabbit model to demonstrate the presence of the estrogen receptor in fibroblasts of the ACL and suggested a dose-dependent relationship between estradiol and the reduction of fibroblast proliferation and collagen synthesis [47] .The authors suggested a potential structural impact on the ACL especially prior to ovulation when estradiol levels are highest **(Figure 1)**[47]. Other studies in humans have supported this theory, showing varying degrees of knee laxity, as measured by arthrometer, in females at different stages of the menstrual cycle, with knee laxity at its maximum during ovulation, thus suggesting a potential increase in knee joint loading and subsequently increased risk of ACL rupture during aggravating athletic maneuvers [48-52]. However, these results have conflicted with other studies showing similar levels of knee laxity observed in female athletes across all phases of the menstrual cycle, thereby indicating the need for future investigations with larger populations to better elucidate whether the biomechanics of the knee joint are altered based on menstrual cycle phase and endogenous estrogen levels [53, 54]. Additionally, a small study observed a greater degree of hamstring extensibility, a property though to reduce knee stability, in women during ovulatory phase versus other phases in the menstrual cycle [55].

Studies have shown disproportionate rates of ACL injuries in female athletes between the three phases of the menstrual cycle [56-60]. A systematic review of 7 articles by Hewett et al. demonstrated ACL injuries in the preovulatory phase of the menstrual cycle, where estrogen levels are rapidly rising, versus post-ovulatory phase where estrogen levels are relatively constant or decreasing **(Figure 1)**[58]. Another study by Lefevre et al. involving 172 women who skied recreationally obtained the date of last menstrual period (LMP) through a questionnaire and classified patients based on their menstrual phase[56]. The authors demonstrated a significantly higher incidence of ACL injuries occurring during the ovulatory phase where estrogen levels are highest, relative to follicular and luteal phase, as well as a 2.4 times increased frequency of ACL injuries in the pre-ovulatory phase[56]. These results have been supported by multiple other studies that have demonstrated a significant increased incidence of ACL injuries either at ovulation or directly preceding ovulation, with less frequent ACL injuries in the follicular and luteal phases of the menstrual cycle where estrogen levels are relatively lower[57, 59-61]. In addition to increased knee laxity observed at ovulation, greater knee valgus moments during landing and femoral internal rotation have been observed during the ovulatory phase and proposed as possible mechanisms related to serum estrogen levels in female athletes [62]. Interestingly, a study involving men who had non-contact knee injuries observed a significantly higher concentration of salivary estradiol in those with ACL injuries [63].

Figure Legends:



Note. Adapted from "The Effects of Menstrual Cycle Phase on Exercise Performance in Eumenorrheic Women: A Systematic Review and Meta-Analysis." by McNulty, K.L., Elliott-Sale, K.J., Dolan, E. et al. Sports Med 50, 1813–1827 (2020). https://doi.org/10.1007/s40279-020-01319-3

Figure 1: *Schematic of Estrogen Levels at Various Phases throughout the Menstrual Cycle*

Relaxin

Relaxin is a peptide hormone produced most prominently released in the post-ovulatory period and has been implicated in loosening the pubic symphysis to facilitate labor as well as altering the biomechanical properties of pelvic ligaments to promote flexibility and laxity[64, 65]. The mechanism through which relaxin alters ligaments is thought to occur through the expression of matrix metalloproteinases (MMP) that catalyze the breakdown of collagen [66]. A previous in vitro study identified the presence of relaxin receptors in the ACL of women, with no evidence of their presence in male ACL tissue[67]. Female ACL tissue treated with relaxin after priming with estrogen exhibited increased expression of MMP-1 and MMP-3 without similar effects observed in male ACL tissue likely due to the absence of relaxin receptors [68]. The increased levels of MMP in ACL tissue after exposure to relaxin may provide a mechanism for breakdown of collagen and reduced biomechanical strength of the ACL tissue, and may explain variations seen in injury rates throughout the menstrual cycle [68]. However, as relaxin levels are thought to peak by the end of luteal phase and prior to menstruation, this conflicts with previous reports noting increased incidences of ACL injuries in the ovulatory phase and preovulatory phases, suggesting other contributory mechanisms[56-60, 64].

Testosterone

The role of testosterone in altering the biomechanics of the ACL has been controversial [69]. It has been suggested that higher levels of testosterone can lower knee laxity and increase tendon stiffness thus having a protective effect in preventing ACL injury [69]. Additionally, data from animal models suggests that testosterone indirectly blocks the expression of relaxin receptors, which may possibly suppress induction of ligament laxity [69]. However, results have not been uniform, with a different study suggesting that levels of serum testosterone have a positive correlation with ACL ligament laxity, similar to estrogen [63].

Use of Oral Contraceptive Pills (OCP)

Oral Contraceptive Pills (OCPs) prevent ovulation through suppression of follicular stimulating hormone (FSH), and luteinizing hormone (LH), and thereby prevent the increase in endogenous estrogens observed in the ovulatory phase **(Figure 1)**. Although multiple OCP regimens exist in clinical practice, the typical regimen involves a steady concentration of exogenous estradiol delivered by the medication throughout the entire menstrual cycle that mimics the luteal phase, followed by a period of estrogen withdrawal in the final week while taking inert pills. As such, the levels of circulating estrogen typically do not exhibit the rapid fluctuations seen in women in the ovulatory phase[70].

Various studies have explored the relationship between women taking oral contraceptive pills and rates of ACL injuries with mixed results. A recent systematic review by Herzberg et al. suggested a protective effect with a 20% reduction in risk of ACL injury in women on OCPs, potentially due to the preclusion of the rapid estrogen fluctuation observed in women undergoing ovulation.[52] Another similar recent systematic review by Konopka et al. agreed with the findings by Herzberg et al. noting decreased risk of ACL injuries and knee laxity with OCP use [31]. This proposition that OCPs exhibit a protective effect and mitigate the risk of ACL injuries has been supported by numerous other studies [71-73]. However, these findings have been challenged by other studies reporting similar rates of ACL injuries between women using OCPs and those without [61, 70]. Given the implications that OCPs can have in potentially preventing or mitigating the risk of ACL injury in female athletes, there is a need for larger and higher quality studies that can better establish this association and can serve to guide physician recommendations to women involved in high-risk athletics who wish to decrease their risk of injury.

Diet, Nutrition, and the Female Athlete Triad

Caloric Intake

The role of diet and nutrition, and whether variation in caloric or nutrient intake can increase the risk of ACL injury is still poorly understood. The female athlete triad has been discussed in literature and consists of amenorrhea, disordered eating, and osteoporosis [74-76]. This constellation of symptoms is common among young female athletes who aim to control their weight and reduce body fat for better athletic performance, pressure from coaches, or other personal reasons and may be associated with eating disorders. Previous studies have implicated reduced bone health and hypoglycemia in this group, suggesting a detrimental impact on not only athletic performance, but overall health [74, 76, 77]. A study by Edama et al. assessed female collegiate athletes for the female athlete triad criteria based on menstrual history, percent of ideal body weight, and bone density measured using a sonographic densitometer and reported incidence of sport related injuries [75]. The authors noted higher risk of injuries in athletes with evidence of energy deficiency [75]. Further studies are needed to see if such results translate specifically to ACL injuries, as interventional measures to screen, identify, and provide support to female athletes with nutritional deficiencies can serve as a potential risk mitigation strategy.

Diet and Endogenous Estrogen

The role of diet in relation to circulating endogenous estrogen levels has also been discussed in literature [78-81]. Western diets have been implicated in higher plasma levels of estradiol and estrone [78]. As discussed previously, elevated serum estrogen may contribute to increased ACL laxity creating a predisposition for injury and as such diets promoting greater levels of circulating endogenous estrogens may negatively impact female athletes. A study by Rose et al. noted that diet supplementation with wheat bran can reduce levels of serum estrogen in the follicular and luteal phases of the menstrual cycle. While in theory such dietary changes may reduce levels of endogenous estrogens, it is important to note the relative lack of randomized or cohort studies in literature that directly compare the rates of ACL injury between different diet types, and precludes definitive conclusions on this topic, and presents avenues for future research.

Vitamins and Minerals

Few studies have reported on vitamin supplementation in patients with ACL injury with conflicting results. A case series by Gupta et al. explored the role of Vitamin D deficiency in athletes undergoing ACL reconstruction and noted no association between deficiency and subsequent rupture of graft or functional outcomes in patients. [82] Another study examined the efficacy of Vitamin C supplementation through joint irrigation in an animal model and noted improvements in graft incorporation in the first 6 weeks postoperative, however results were similar between the Vitamin C supplementation group and controls at 42 weeks [83]. Additional human studies are needed to better elucidate whether such Vitamin supplementation can be beneficial to patients postoperatively after ACL reconstruction.

Injury Prevention Programs for Female Athletes

Given the increased relative risk of ACL injury in female athletes compared to male athletes, the development of effective injury prevention programs tailored to address risk factors in female athletes is of particular interest. Various types of injury prevention programs have been described in literature with multicomponent neuromuscular training programs as the most prominent and directed hamstring eccentric strength training to a lesser degree.

Neuromuscular and Proprioceptive Training Programs

The goal of neuromuscular and proprioceptive training programs is to correct abnormally coordinated lower extremity movements and thereby prevent high risk maneuvers that can create an incidence of ACL injury.[84] Various forms of neuromuscular training have been identified in literature including balance, plyometric, strength, and running exercises, and landing technique and are often used in combination with one another[84]. Multiple previous meta-analyses have implicated neuromuscular training as protective for ACL injury in female athletes particularly those involving multiple components [84-88]. A recent systematic review and meta-analysis reviewed all randomized control trials studying injury prevention programs among groups of ≥20 female soccer players with outcomes related to ACL injury incidence published until August 2019. Nine studies reviewed instituted a multi-exercise neuromuscular training programs, 1 instituted balance board training, eccentric hamstring exercises, and 1 instituted the use of a smaller, lighter soccer ball and noted that these multicomponent, exercise-based programs reduced the incidence of ACL injuries by 45%[89] While this result is promising, the reviewed RCTs all suffered from high risk of bias and the effectiveness of injury prevention programs have been called into question due to their benefit being highly reliant on proper implementation and long-term compliance, which tends to degrade over the course of a season [89-91]. Furthermore, the heterogeneity between different neuromuscular programs is not ideal, and can make it difficult to provide clinical guidelines on which set of exercises provide the most benefit to female athletes.[43, 89] A recent meta-analysis by Petushek et al. attempted to clarify specific components of through a meta-regression model and noted that exercises focusing on lower body strength training with emphasis on landing techniques were optimal for preventing ACL injuries [43]. That said, higher quality studies, especially those directly comparing different neuromuscular training regimens, as well as incorporating supplementary variables such as athlete compliance are needed to better assess the effectiveness of implementation of such programs and allow for optimal training program design.

Directed Hamstring Strength Training

Correction of the relatively lower H/Q ratio in female athletes through strength training presents an opportunity for injury prevention program design [43]. As mentioned previously, lower H/Q ratios indicate a weakness of the flexor mechanism that is thought to stabilize the knee joint and prevent ACL shearing during knee extension and anterior translation particularly during landing [30, 39, 41, 92]. Previous suggested the use of hamstring strengthening as a measure to better equalize the relative strengths of the knee flexors and extensors and reduce the risk of primary ACL injury and reinjury, however future studies are needed that directly compare incidence rates of ACL injuries in athletes undergoing preventative hamstring strength and those without to better elucidate whether the integration of these exercises in an injury prevention regimen produces clinically significant outcome[93-95].

Discussion

Current literature suggests that the increased risk for ACL injury in females is multifactorial, likely influenced by a combination of anatomical and hormonal factors more predominant in females versus males. Anatomical factors identified as potentially contributing to this increased risk of ACL rupture in females included narrower intercondylar notch widths, wider pelvic widths, and increased Q angles although whether these factors are truly contributory is currently debated. Lower H/Q ratios in women as well as greater hip and knee range of motion serve as other potential anatomical risk factors for ACL injury.

Additionally, fluctuations in hormones such as estrogen and relaxin throughout the menstrual cycle are thought to contribute to biomechanical changes in the ACL that predispose women to ACL rupture. The role of diet and nutrition in creating a predisposition for ACL injury is less understood, however previous studies have shown increased risk of general sports related injuries in female athletes that met criteria for the female athlete triad characterized by caloric and nutritional deficiency. Additionally, western diets are implicated in increasing endogenous estrogens which can in theory increase risk of ligament laxity and therefore the risk of ACL rupture. Whether dietary recommendations can be given to prevent ACL injury is debatable, however further research performed in this topic can serve to guide clinician recommendations for female patients seeking to mitigate their risk of injury.

Various injury prevention programs for female athletes have been identified, the most prominent of which is neuromuscular training, and however a great degree of heterogeneity exists in program design which precludes the ability to provide definitive clinical recommendations. Comparative studies across various standardized injury prevention programs can present areas for future research studies to better elucidate the crucial components of effective programs and guide optimal injury prevention program design.

Conclusion

In female athletes, a constellation of anatomic, hormonal, and dietary factors can play a role in increasing the risk of ACL injuries. While certain risk factors such as those related to anatomy are inevitable, future research in this field can provide a better understanding on the degree of risk conferred from hormonal and dietary factors and guide clinicians in providing recommendations on risk mitigation strategies to female athletes involved in high-risk sports. Additional, more extensive comparative studies into injury prevention programs can identify crucial components and guide effective program design.

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