Sexual Dimorphisms in Anterior Cruciate Ligament Injury

A Current Concepts Review

Tayt M. Ellison,*† MD, Ilexa Flagstaff,‡ MD, and Anthony E. Johnson,§ MD

Investigation performed at Department of Orthopaedics, San Antonio Military Medical Center, Joint Base San Antonio–Fort Sam Houston, San Antonio, Texas, USA

Background: Although most anterior cruciate ligament (ACL) injuries occur in male athletes, female athletes are consistently observed to be at a higher risk for sports-specific ACL injury.

Purpose: To provide a thorough review of what is known about the sexual dimorphisms in ACL injury to guide treatment and prevention strategies and future research.

Study Design: Narrative review.

Methods: We conducted a comprehensive literature search for ACL-related studies published between January 1982 and September 2017 to identify pertinent studies regarding ACL injury epidemiology, prevention strategies, treatment outcomes, and dimorphisms. By performing a broad ACL injury search, we initially identified 11,453 articles. After applying additional qualifiers, we retained articles if they were published in English after 1980 and focused on sex-specific differences in any of 8 different topics: sex-specific reporting, difference in sports, selective training, hormonal effects, genetics, neuromuscular and kinematic control, anatomic differences, and outcomes.

Results: A total of 122 articles met the inclusion criteria. In sum, the literature review indicated that female athletes are at significantly higher risk for ACL injuries than are their male counterparts, but the exact reasons for this were not clear. Initial studies focused on intrinsic differences between the sexes, whereas recent studies have shifted to focus on extrinsic factors to explain the increased risk. It is likely both intrinsic and extrinsic factors contribute to this increased risk, but further study is needed. In addition to female patients having an increased risk for ACL injuries, they are less likely than are male patients to undergo reconstructive surgery, and they experience worse postsurgical outcomes. Despite this, reconstructive surgery remains the gold standard when knee stability, return to sports, and high functional outcome scores are the goal, but further research is needed to determine why there is disparity in surgical rates and what surgical techniques optimize postsurgical outcomes for female patients.

Conclusion: Male athletes often predominated the research concerning ACL injury and treatment, and although sex-specific reporting is progressing, it has historically been deficient. ACL injuries, prevention techniques, and ACL reconstruction require further research to maximize the health potential of at-risk female athletes.

Keywords: knee; ACL; female athlete; medical aspects of sports; anatomy; epidemiology

Approximately 120,000 anterior cruciate ligament (ACL) injuries occur annually, with a peak incidence in the adolescent to young adult years. While male athletes account for most injuries in the general population (because of their greater exposure to athletic tasks predisposing them to ACL injury), female athletes are consistently observed to be at higher risk for sports-specific injury. While the reported ratios of female-to-male ACL injury range from 2:1 to as high as 9:1, variability exists by sex and sport, as well as response to mitigation via injury reduction training programs. The exact reasons for this discrepancy are not fully known.

Figure 1 stratifies the studies included in this review by topic. Early studies focused heavily on hormonal, anatomic, and genetic difference but these studies did not definitively account for the discrepancy. As such, most recent studies have shifted to focus on kinematics and sport-specific training, which also have not fully accounted for the discrepancy. We hypothesized that any disparity in the incidence of ACL injuries between male and female athletes was multifactorial, resulting from both intrinsic (biochemical, hormonal, neuromuscular, kinematic, and anatomic differences) and extrinsic factors (differing sports and a selective training bias). The
consequences of ACL injury can be physically, psychologically, and financially significant—both in the short and the long term. The average cost of an ACL injury ranges from $17,000 to $25,000. Further, such injuries frequently result in loss of athletic scholarships, loss of competitive season or career, and decreased productivity in the short term and posttraumatic osteoarthritis in the long term.

Although the rates of ACL reconstruction (ACLR) have been increasing for women, with a peak age of reconstruction at 17 years, outcomes vary by sex. Thus, thorough understanding of what is currently known about the differences in ACL injury predilection and mechanisms, prevention strategies, and outcomes of current treatment options between female and male patients is essential to guide treatment and prevention strategies. The purpose of this study was to provide a thorough review of what is known in these areas in order to guide future research.

METHODS

With the assistance of the US Army Medical Department Center and School medical librarians, we conducted a comprehensive literature search to identify pertinent studies published between January 1982 and September 2017 regarding ACL injury epidemiology, prevention strategies, treatment outcomes, and dimorphisms. From this broad search, 11,453 articles were initially identified. Emphasis was placed on recent and higher-level studies with keywords anterior cruciate ligament, sex based, sex differences, gender based, gender differences, and dimorphisms. After applying these qualifiers, articles were retained if they were published in English after 1980. From this extensive literature search, 122 manuscripts were selected.

RESULTS

Sex-Specific Reporting

Female participation in athletics has increased dramatically since the institution of Title IX of the Education Amendments Act of 1972. Between 1982-1983 and 1997-1998, National Collegiate Athletic Association female participation increased by 69%, whereas male participation increased by 3%. As the number of women in sports has increased, so has their incidence of ACL injuries. Although female athletes are reportedly more likely to sustain ACL injuries, the exact difference in incidence among female athletes versus male athletes is not known, as incidence reporting is often not sex specific. Sutton and Bullock reported 100,000 to 250,000 ACL tears per year in the United States but did not separate incidence by sex. A systematic review, including a multicountry analysis, reported the annual incidence of ACL tears among the general population, amateur athletes, and high-level athletes as 0.05%, 0.03% to 1.62%, and 0.15% to 3.7%, respectively, but did not discuss sex-based differences in depth.

In 2012, Moses et al, focusing on sex-specific reporting in the literature, asserted male bias exists in research and expressed the importance of its recognition. For example, animal studies predominantly use male participants. In addition, girls and women comprise <40% of participants in clinical trials. For decades, researchers have ignored sex as an affecting variable or have deliberately excluded females to avoid confounders of gestational status and/or the menstrual cycle. To better prevent, diagnose, and treat ACL injuries, it is necessary to study and report sex differences.

Difference in Sports

ACL injury differences between female and male patients have been examined for disparities among sports. The literature has indicated the majority of ACL injuries in female

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*Address correspondence to Tayt M. Ellison, MD, Department of Orthopaedic Surgery, San Antonio Military Medical Center, 3551 Rodger Brook Drive, San Antonio, TX 78234, USA (email: taytellison44@gmail.com).

1Department of Orthopaedics, San Antonio Military Medical Center, Joint Base San Antonio–Fort Sam Houston, San Antonio, Texas, USA.

2Department of Orthopaedics, University of Minnesota, Minneapolis, Minnesota, USA.

3Dell Medical School, University of Texas–Austin, Austin, Texas, USA.

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athletes are noncontact (70%) versus contact injuries (30%).
ACL injuries are of specific concern for multidirectional sports requiring cutting, jumping, and rapid speed changes such as soccer and basketball. As such, most of the literature had focused on sports that require these maneuvers. The risk of an ACL injury in a female collegiate soccer or basketball player is 4.4 to 5% per year as opposed to 1.7% for their male counterparts. Since the enactment of Title IX, female athletes have begun participating in chosen sports at increasingly earlier ages compared with male athletes. Despite this, there has not been a corresponding decrease in female ACL injury rates over the past decade.8

A selective training effect as reasoning for decreased incidence of ACL injuries in male versus female athletes has been proposed. This theory suggests men begin playing their chosen sport at a younger age than women do, resulting in higher proficiency and fewer ACL injuries. However, the evidence supporting this theory has major methodological flaws. Since the enactment of Title IX, female athletes have begun participating in chosen sports at increasingly earlier ages compared with male athletes. Despite this, there has not been a corresponding decrease in female ACL injury rates over the past decade.8

TABLE 1

| Study              | Soccer | Basketball | Other              |
|--------------------|--------|------------|--------------------|
| Arendt and Dick8   | 2.4×   | 4.1×       | Military obstacle  |
|                    |        |            | course: 9.74×      |
|                    |        |            | Rugby: 4×          |
| Lindenfeld et al74 | 3.5×   | —          | —                  |
| Medvecky et al74   | —      | 5.7×       | —                  |
| Mihata et al76     | 2.3-2.9× | 3.5-4.1× | —                  |
| Mountcastle et al78| 0.84×  | 2.4×       | Gymnastics: 5.67×  |
|                    |        | 1.27×a    | Obstacle course: 3.72×a |
| Prodromos et al87  | 2.67×  | 3.5        | Wrestling: 4.05×   |
| Stanley et al101   | 2.8×   | 3.25×      | —                  |

aNoncontact injury. Dashes indicate no data reports/none reported.

Selective Training

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Although Silvers and Mandelbaum90 suggested selective training decreases ACL injury risk, they also suggested selective training must be optimally implemented, noting a minimum of 6 to 8 weeks is required to achieve a neuro-muscular effect. A number of operationally relevant inquiries regarding use of selective training to reduce ACL injury risk remain, including the optimum timing of specific training within the sports season (eg, preseason, season, off-season); prevalence of degradation and necessity, if any, of retraining; differences for training the novice versus the experienced athlete; and whether the training effects and requirements are amenable to universal application or exhibit variation based on sex, sport, and skill level.

TABLE 2

| Study              | Follicular Phase | Ovulatory Phase | Luteal Phase |
|--------------------|-----------------|----------------|-------------|
| Increased risk of ACL injury | Arendt et al9 | Wojtys et al10 | Myklebust et al80 (early follicular) |
|                    | Myklebust et al80 (late luteal) | Wojtys et al117 | Slauntherbe and Hardy98 |
| Increased ACL laxity | —              | Park et al83   | Deie et al86 |
|                    | —              | Heitz et al143 | Shultz et al95 |
| Increased strength and fatigue, decreased relaxation | — | Sarwar et al92 | — |

aACL, anterior cruciate ligament. Dashes indicate no data reports/none reported.

Hormonal Effects

Hormones are one of the most readily apparent differences between male and female athletes. As such, much of the research on endocrine effects on the ACL has focused on cycling hormone levels during the menstrual cycle—mainly estrogen and relaxin. Estrogen receptors are present on ACL fibroblasts, which produce collagen, the main tensile strength component for the ACL. It is suspected that when estrogen is abundant, collagen production increases, reducing tissue water content, disrupting ligamentous stability. Relaxin decreases ligamentous tensile strength via release of metalloproteases leading to collagen breakdown. Thus, these hormones may play a direct role in weakening the ACL, possibly leading to an increase in female ACL injury. However, the effects of cycling levels of estrogen and relaxin on knee joint laxity, mechanics, and muscle control are not well defined. As demonstrated in Table 2, although multiple studies have indicated increased ACL injury or laxity during different phases of the menstrual cycle, there is little consensus as to which phase, if any, puts the ACL at most risk. Further, studies have often measured different outcomes, injury versus laxity, making them difficult to compare. The clinical correlation between knee laxity and its risk for ACL injury rates is unclear. Although Park et al84 found there was a significant difference in knee laxity throughout the menstrual cycle, they reported it did not lead to clinically significant changes in knee-joint mechanics or any increased risk of ACL injury. Sarwar et al92 found increased quadriceps strength and fatigability with decreased relaxation during ovulation. Further, Shultz et al95 advocated research be guided to look at the
menstrual cycle phase 3 to 4 days prior to the increase in laxity as the culprit for increased laxity due to the dose-dependent antagonist effect of estrogen and the 3- to 7-day delay in tissue modulation.\textsuperscript{120} Finally, other studies have found no discernible relationship between the menstrual cycle and knee laxity, stiffness, or muscle strength.\textsuperscript{22,54,57}

The effect of relaxin on ACL laxity and injury rates is also not yet well defined. Dragoo et al\textsuperscript{31} identified relaxin receptors only in female patients, leading some to believe this to be a major difference between female and male ACL injury. They found a relationship between relaxin concentration and ACL injury. Elite collegiate athletes sustaining ACL tears had significantly higher risks when their serum relaxin concentrations were increased and 4 times higher risk when concentrations reached 6.0 pg/mL. However, Arnold et al\textsuperscript{11} and Wolf et al\textsuperscript{118} reported no relationship regarding genetic effect on ACL injury has continued, sex-specific reporting has increased. Table 3 summarizes current genetic research supporting the hypothesis that differences in female versus male genetic makeup contribute to differing risk of ACL injury. Although it is important to discover genetic risk factors for ACL injury to identify individuals at risk, obviously genetic makeup is a nonmodifiable risk factor. In order to develop targeted therapies, genetic research should strive to identify and determine whether specific genes predispose to, or protect from, ACL injury.

### Genetics

| Study | Gene | Effect |
|-------|------|--------|
| Johnson et al\textsuperscript{25} | WISP2 (Wnt-1-inducible signaling-pathway protein-2) | WISP2: decreased expression in female patients with ACL injury |
|       | FMOD (fibromodulin) | FMOD, ACAN: increased expression in female patients with ACL injury |
|       | ACAN (aggrecan) | |
| Posthumus et al\textsuperscript{86} | COL5A1/COL12A1 (collagen5a1/ collagen12a1) | Increased expression in female patients with ACL injury |
| Rahim et al\textsuperscript{88} | KDR (kinase insert domain receptor) | Protective in female patients against ACL injury |

\textsuperscript{aACL, anterior cruciate ligament.}

Neuromuscular control and kinematic control are important modifiable risk factors in the dichotomy between male and female ACL injury.\textsuperscript{62} There are multiple hypotheses to explain this observation that include (1) estrogen possibly altering neuromuscular control with increased quadriceps strength\textsuperscript{62} and (2) hamstring-quadriceps imbalance possibly leading to improper dynamic knee stabilization in women.\textsuperscript{3,24,44,62,79} However, Bennett et al\textsuperscript{115} reported an imbalance in the hamstring-quadriceps ratio not being a significant predictor of anterior tibial shear force.

Female athletes also demonstrate greater valgus moment arms during landing and cutting maneuvers that place undue stress on the ACL.\textsuperscript{13,18,35,44,73,82} These valgus moments are worsened by the point of maximal height velocity.\textsuperscript{46} Finally, Leetun et al\textsuperscript{61} reported that the lack of core and hip stabilization in young girls, specifically hip abduction weakness, is a predictor of lower extremity injury. These risk factors, however, can be modified. Orishimo et al\textsuperscript{62} reported female dancers not demonstrating the neuromuscular and kinematic deficits that female team sports athletes do, suggesting that early training in proper landing technique, strength, and core stabilization in prepubertal female athletes can decrease ACL injuries.\textsuperscript{56,61} Longitudinal study of ACL injury prevention programs is required to definitively determine the effect of

Neuromuscular and Kinematic Control

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neuromuscular control and kinematics on the incidence of ACL injury.

Anatomic Differences

The anatomic differences between female and male participants have been intensely researched without solid conclusions as to which differences, if any, increase risk of ACL injury in female participants. Tables 4 and 5 outline ACL anatomic differences between female and male participants along with the studies finding whether specific anatomic differences are increased risk factors for ACL injury. As is apparent from the tables, research has not demonstrated a clear-cut anatomic difference accounting for increased incidence of ACL injury in female patients. Further, as anatomic differences are nonmodifiable risk factors, their use may be limited in designing prevention programs. Some authors have proposed that the measurements be used as a screen to identify athletes at risk and then pursue neuromuscular and kinematic training intervention.44

Outcomes

Sex-specific reporting in outcome measures is important in determining the appropriate surgical intervention. Mall et al70 reported that between 1996 and 2006, the incidence of ACLR nearly doubled, with the fastest growing populations being female and patients <20 years of age. Leathers et al60 found the overall incidence of ACLR increased in the United States by 16.9% between 2004 and 2009 and male patients underwent the procedure twice as often as female patients despite the higher incidence of female ACL injury. The reasons for this gap, which could include unconscious bias favoring surgery for male patients at the patient-physician level, are unknown and require further study.

Just as the cause of ACL injury disparity between female and male patients is not well defined, ACLR outcome measures are, likewise, not well defined. Table 6 demonstrates the considerable variability of research findings regarding ACLR outcome measures between female and male patients. Multiple authors have suggested poorer outcomes and increased rates of contralateral injury and graft rupture in female patients, opining such to be due to continued poor neuromuscular control and kinematic deficits.24,27,58 In contrast, Tan et al,105 in a comprehensive and systematic review of 120,000 patients, found graft rupture/rerupture rates were not influenced by sex but also concluded that female patients had overall poorer outcomes, reflected in lower return-to-sports rates and lower functional outcome scores. Thompson et al107 also found poor return-to-sport outcomes in female patients, whereas, Howard et al56 found that younger college athletes with scholarship have higher

| TABLE 4 |
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| Literature in Favor of or Against Specific Anatomic Differences as Contributing Factors to Sex-Based Disparity in ACL Injuries<sup>a</sup> |

| Anatomic Variable | In Favor | Against |
| --- | --- | --- |
| Posterior Tibial Slope Notch Width ACL Volume/Cross-sectional Area | Beynnon et al<sup>17</sup> | Meister et al<sup>75</sup> |
| Notch Width | Anderson et al<sup>16</sup> | Domzalski et al<sup>30</sup> |
| | Emerson<sup>32</sup> | Everhart et al<sup>93</sup> |
| | Hoteya et al<sup>47</sup> | Lund-Hanssen et al<sup>68</sup> |
| | Shelbourne et al<sup>94</sup> | Simon et al<sup>97</sup> |
| | Souryal and Freeman<sup>99</sup> | Stournick et al<sup>103</sup> |
| | Uhorchak et al<sup>110</sup> | Van Eck et al<sup>112</sup> |
| | Whitney et al<sup>115</sup> | Wolters et al<sup>119</sup> |
| | Zeng et al<sup>122</sup> | |

<sup>a</sup>ACL, anterior cruciate ligament.

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| Literature in Favor of Other Anatomic Variables as Contributing Factors in the Sex-Based Disparity in ACL Injuries<sup>a</sup> |

| Anatomic Variable | Study |
| --- | --- |
| Q angle | Zelisko et al<sup>121</sup> |
| Thigh length | Beynnon et al<sup>16</sup> |
| ACL tensile properties | Chandrashekar et al<sup>23</sup> |
| Notch size/ACL size mismatch | Johnson et al<sup>55</sup> |
| Femoral notch ridge size | Whitney et al<sup>115</sup> |
| Meniscal slope | Meister et al<sup>75</sup> |

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| Lipps et al<sup>65</sup> | |
| Markolf et al<sup>71</sup> | |
| Simon et al<sup>97</sup> | |
| Stournick et al<sup>103</sup> | |
| Todd et al<sup>108</sup> | |
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TABLE 6
Literature on Sex-Specific Differences in Outcome Measures After ACLR

| Contralateral ACL Tears                                                                 |
|----------------------------------------------------------------------------------------|
| No Difference                                                                          |
|                                         Increased Tears                                    |
|                                         in Female Patients                                 |
|                                         Increased Tears                                    |
|                                         in Male Patients                                  |
| Andernord et al[4]                                                                     |
| Brophy et al[21]                                                                       |
| Kaeding et al[56]                                                                      |
| Ryan et al[90]                                                                         |
| Thompson et al[107]                                                                    |
| Webster et al[114]                                                                    |
| Ahldén et al[2]                                                                        |
| Putero et al[45]                                                                      |
| Shelbourne et al[94]                                                                  |
| None reported                                                                          |

| Graft Ruptures                                                                         |
|----------------------------------------------------------------------------------------|
| No Difference                                                                          |
|                                         Increased Ruptures                                    |
|                                         in Female Patients                                 |
|                                         Increased Ruptures                                    |
|                                         in Male Patients                                  |
| Andernord et al[4]                                                                     |
| Ferrari et al[34]                                                                      |
| Kaeding et al[56]                                                                      |
| Lyman et al[108]                                                                       |
| Ryan et al[90]                                                                         |
| Salmon et al[91]                                                                       |
| Shelbourne et al[94]                                                                  |
| Spindler et al[100]                                                                   |
| Tan et al[105]                                                                         |
| Slaulerbeck and Hardy[28]                                                               |
| Bourke et al[19]                                                                       |
| Leys et al[19]                                                                         |
| Thompson et al[107]                                                                    |
| Webster and Feller[13]                                                                 |

| Return-to-Play Rate                                                                   |
|----------------------------------------------------------------------------------------|
| No Difference                                                                          |
|                                         Decreased Rate                                     |
|                                         in Female Patients                                 |
|                                         Decreased Rate                                     |
|                                         in Male Patients                                  |
| None reported                                                                         |
| Ardern et al[7]                                                                        |
| Brophy et al[21]                                                                       |
| Tan et al[105]                                                                         |
| Thompson et al[107]                                                                    |

| Functional Outcome Scores                                                              |
|----------------------------------------------------------------------------------------|
| No Difference                                                                          |
|                                         Lower Scores                                     |
|                                         in Female Patients                                 |
|                                         Lower Scores                                     |
|                                         in Male Patients                                  |
| Ahldén et al[2]                                                                        |
| Barber-Westin et al[12]                                                                |
| Ferrari et al[34]                                                                      |
| Salmon et al[91]                                                                       |
| Spindler et al[100]                                                                    |
| Tohyama et al[109]                                                                     |
| Ageberg et al[1]                                                                       |
| Tan et al[105]                                                                         |
| Thompson et al[107]                                                                    |
| None reported                                                                         |

**a**ACL, anterior cruciate ligament; ACLR, anterior cruciate ligament reconstruction.

The return-to-play rates unrelated to graft type, tunnel placement and concomitant surgical procedures.

Despite female patients being reported as having worse postsurgical outcomes compared with male patients, it is agreed that ACLR is the gold standard when knee stability, return to sports, and high functional outcome scores are the goal. The appropriate surgical technique, graft choice, and tunnel placement and their sex-specific outcomes, however, remain elusive. Thompson et al[107] reported a patellar tendon graft choice in female patients leading to an acceptable decline in failure rates. However, it may lead to other complications contributing to decreased return to sports among these female athletes. More research is needed to investigate whether graft choice has a significant effect on outcomes for female versus male athletes.

**CONCLUSION**

Our review of the literature has shown that the ratio of female to male athletes sustaining an ACL injury ranges from 2:1 to 9:1. However, the exact reasons for this disparity have not been fully elucidated. Male patients often predominate the research concerning ACL injury and treatment, and although it is progressing, sex-specific reporting is historically deficient. It is important to understand that ACL injuries, prevention techniques, and ACLR are sex specific.

To better define the difference between women and men, sex-specific ACL tear incidence reporting must be encouraged. Further, to better delineate the sexual dimorphisms in ACL injuries to guide treatment and prevention strategies, more research and inquiry is needed as to the effect of selective training based on sex, sport, and skill level; the effects of hormones, hormone cycling and hormone modification on ACL injury; genetic risk factors for ACL injury stratified by sex; and anatomic differences between male and female patients relating to ACL injury.

Further, longitudinal investigation into the modifiable risk factors is most important to identify those at risk, modify their neuromuscular and kinematic deficits, and lower overall ACL injury rates. Improved outcomes would lead to decreased functional loss, decreased loss of scholarships, a decline in long-term osteoarthritis, and decreased cost of ACLR and rehabilitation.

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