

Factors and Mechanism of High Incidence of Anterior Cruciate Ligament Injury in Women

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Abstract:

Anterior cruciate ligament (ACL) injury is a common serious knee injury in sports medicine, prevalent in high-intensity sports involving sudden stops, direction shifts and jumping. Epidemiological data indicate female ACL injury incidence is 2–8 times higher than males, alongside poorer rates of return to competitive sport post-injury. This gender disparity is a core research topic in sports injury prevention, with existing studies examining anatomical, molecular physiological and biomechanical contributors. Distinct female osseous knee traits including elevated tibial posterior slope and narrower femoral intercondylar notches raise ligament mechanical loading and injury vulnerability. Cyclic estrogen secretion disrupts ligament tissue remodeling and mechanical stiffness. Transcriptomic testing reveals sex-dependent extracellular matrix homeostasis regulation: ACAN, FMOD are upregulated while WISP2 is suppressed in female ACL tissue. During landing and cutting motions, females present abnormal lower-limb kinematics that trigger excessive knee valgus, elevated abduction torque, flexor-extensor muscle activation imbalance and reduced knee dynamic stability. Hormone swings during ovulation impair lower-limb neuromuscular control, creating a high ACL injury-risk window. Though individual risk factors are documented, their synergistic interactions and unified gender-specific injury mechanisms remain unclear, with no gender-tailored standardized clinical intervention frameworks. This review synthesizes multi-factor ACL injury mechanisms in females, summarizes current evidence gaps, and informs future research on gender-linked knee injuries.

Keywords: Anterior cruciate ligament injury, female athlete, knee biomechanics, estrogen, sports injury prevention.

1. Introduction

Anterior cruciate ligament (ACL) injury is one of the most common knee injuries with high disability in the field of sports medicine, especially in non-contact movements such as directional running and emergency stop. The incidence of ACL injury in women is 2-8 times that of male athletes. In high-intensity antagonistic sports such as basketball and football, the incidence of ACL injury in women can be 2 to 5 times higher than that in men. This significant gender difference indicates that more attention should be paid to the mechanism of anterior cruciate ligament injury in women.

Complete anterior cruciate ligament rupture may lead to acute and chronic physical and mental illness, such as anterior knee pain, osteoarthritis, fear of re-injury, and missed time for exercise and physical exercise, accompanied by high medical costs. And it may take up to 6 months to 1 year of rehabilitation period, but also can cause knee joint degenerative disease, seriously weaken the motor function, shorten the sports life of athletes [1]. Despite the use of modern surgical techniques, only 65 % of athletes can recover to the pre-injury level after anterior cruciate ligament rupture, and only 55 % can return to competitive competition. The possibility of men returning to the pre-injury competitive level after anterior cruciate ligament rupture is 1.7 times that of women [2].

The gender difference in the risk of ACL injury, the internal mechanism of which is likely to be the result of multiple factors. At present, a variety of hypotheses have been proposed to explain the pathophysiological basis of this difference, including internal factors such as anatomical structure, hormone level, neuromuscular control and biomechanical characteristics, as well as several external environmental factors. The purpose of this paper is to systematically sort out the gender influencing factors related to the pathogenesis of ACL injury, in order to provide a theoretical basis for the development of targeted preventive intervention strategies for high-risk groups [3]. This study integrates anatomical, hormonal and biomechanical dimensions to categorize gender-dominated pathogenic factors of ACL injury, rather than relying on a single influencing dimension in previous researches. On the basis of sorted gender differences, this research supports the formulation of differentiated prevention schemes, which realizes precise intervention for susceptible female athletes and other high-risk cohorts.

2. Explain the Reasons for the High Incidence of Women from the Perspective of Anatomy, Genes, Hormones and Biomechanics

2.1 Anatomical differences

At the anatomical level, the female knee joint showed a clear gender dimorphism : the tibial plateau area was small, the femoral notch was narrow, the ACL volume and the cross-sectional area of collagen fibers were lower than those of men.

The load transfer of the knee joint is affected by the anatomical structure of the bone and articular surface. In the sagittal plane of the normal knee joint, the tibial plateau is tilted backward and forward, which is called the posterior slope of the tibial plateau (PTS). It is defined as the angle between the vertical line perpendicular to the long axis of the tibia and the tangent line along the sagittal slope of the tibial plateau.

Studies have confirmed that the posterior slope of the tibial plateau in women is generally greater than that in men, and it is more likely to have the anatomical characteristics of increased posterior slope. However, the effects of medial and lateral tibial plateau posterior slope angles on knee joint mechanics are not the same, and the lateral tibial plateau posterior slope angle can be used as an independent risk factor for injury. When the posterior slope of the lateral tibial plateau is greater than that of the medial, the tibia will rotate internally under the weight-bearing state of the human body.

After carrying out the simulated acute landing test, Lipps et al. found that women not only had a higher posterior slope of the lateral tibial plateau than men, but also had a greater internal rotation of the tibia during the simulated landing process, and the strain value of the anterior cruciate ligament (ACL) was also higher. The research team put forward the hypothesis that the increase of tibial mobility and the increase of anterior cruciate ligament stress were caused by the large posterior slope angle of the lateral tibial plateau.

2.2 Genetic differences

In recent years, scientists have accurately captured the differences in gene expression between male and female ACL tissues through cutting-edge technologies such as single-cell sequencing.

A study compared gene expression and structural features in ruptured but otherwise normal anterior cruciate ligament tissues of young male and female samples of ruptured anterior cruciate ligament were collected from

seven female and seven male athletes (aged 12.7 to 22.6 years). Each sample was divided into several parts for histological and gene expression analysis. Samples used for genetic analysis were frozen and ground, and RNA was extracted and purified. RNA microarray analysis was performed on four female and three male (age 13.9-18.5 years) non-contact injury participants. IPA software (Qiagen) was used to group these genes with significantly different expression levels between female and male athletes into functional-related networks. Through RT-qPCR (transcription quantitative polymerase chain reaction) analysis, three genes of interest were selected for further verification, covering all 14 patient samples. A variety of statistical methods were used to examine gender-related analysis of RNA isolated from the ruptured anterior cruciate ligament tissue of male and female athletes revealed 32 genes with significant differential expression. Among them, 14 genes were not associated with X or Y chromosomes. IPA analysis classified these genes into pathways involved in skeletal muscle development and function, as well as cell growth, maintenance and proliferation. RT-qPCR confirmed that the expression of the three selected genes was significantly different: ACAN and FMOD (fiber regulatory protein) were up-regulated in women compared with men, and WISP2 (1-induced signaling pathway protein 2) was down-regulated.

The genes identified in this study were significantly different due to gender, resulting in the main molecules in the extracellular matrix of the anterior cruciate significant up-regulation of ACAN and FMOD of the regulatory matrix, as well as the down-regulation of WISP2 involved in collagen renewal and production, may explain the reason why women's anterior cruciate ligament is weaker than men [4].

2.3 Hormone Differences

The difference in sex hormone levels is considered to be a key potential factor leading to the gender-dependent response of ACL to mechanical load.

Studies have shown that estrogen receptors are expressed in ACL fibroblasts of both men and women, and that estrogen can regulate multiple genes related to soft tissue, the specific direction and effect strength of the existing literature on the effect of estrogen on the mechanical properties of ACL have not yet been agreed. Nevertheless, clinical observations provide strong indirect evidence that knee joint relaxation changes significantly with the fluctuation of estradiol concentration during the menstrual cycle in women, with an average change of up to 3 mm. Considering that if the asymmetry of the left and right sides of the knee joint reaches 1.3mm, the risk of ACL injury will

increase by four times. This hormone-induced relaxation fluctuation is likely to partially explain the phenomenon that the rate of ACL injury in women is significantly higher than that in men. Further studies have found that inhibiting the periodic peak of estrogen by oral contraceptives can effectively reduce the periodic changes of knee joint relaxation, which provides supportive evidence for the direct effect of estrogen on the mechanical properties of ACL tissue [5].

In order to further explore the performance of the above mechanisms in dynamic sports, a study recruited 25 female football and basketball players with regular menstrual cycles. Each subject's early follicular, ovulatory and midluteal phases were accurately determined by hormone detection combined with a calendar method. At three time points, the Vicon three-dimensional motion capture system (with two force platforms) and the wireless surface electromyography system were used to synchronously collect the kinematics, dynamics and electromyography data of the subjects when they completed the landing jump and side-cut running movements. The maximum valgus angle, peak abduction torque, ground reaction force, co-activation ratio of hamstring and quadriceps femoris, and activation timing of major muscle groups were analyzed. The data were statistically processed by repeated measures analysis of variance.

The results showed that compared with the follicular phase and luteal phase, athletes showed significantly increased maximum valgus angle ($p < 0.01$) and higher peak abduction torque ($p < 0.05$) during ovulation. During ovulation, the co-activation ratio of hamstring and quadriceps femoris decreased significantly ($p < 0.05$), and the activation intensity of quadriceps femoris increased relatively, indicating that the dynamic stability of knee joint decreased. After the high-intensity interval training in the luteal phase, the athletes showed a trend of decreasing the reaction force index and increasing the level of interleukin-6, indicating that the recovery ability of the stage may be weakened. The data analysis showed that the ovulation period may be the highest risk window for ACL injury due to the increase of ligament relaxation and neuromuscular control deficit, and the early follicular stage was also found to be the high incidence stage of injury.

Based on the above data, the ovulation period is considered to be the 'high-risk window period' with the highest risk of ACL injury due to the superposition of increased ligament relaxation and neuromuscular control deficit, and the early follicular phase is also observed as a high-risk stage of injury. Based on this, this study suggests that the menstrual cycle monitoring mechanism should be introduced into the training and competition management of female athletes, and the neuromuscular control

training dominated by hamstring muscle, landing posture optimization training and fatigue management should be strengthened in the identified high-risk stage, so as to realize the advanced stage of periodic precise protection and provide a scientific and feasible practical scheme for reducing ACL injury rate [6].

2.4 Biomechanical Differences : the Compensation Puzzle of Motion Mode and Torque

Greater valgus angle and adduction moment of knee joint are presented in jumping landing, steering and other movements, and the coordinated activation mode of quadriceps femoris and hamstring muscle is different from that of men. These dynamic differences are considered to be the direct mechanical cause of ACL load increase. ACL injury most often occurs after the disturbance, and the disturbance will cause the athlete to lose balance or out of control, which may eventually lead to leisure athletes were disturbed while walking at a speed of 1.1 m / s. The subject-specific musculoskeletal model was created using motion analysis data, and static optimization was performed in OpenSim to calculate muscle force. Statistical parametric mapping (SPM) was used to compare muscle strength between men and women during the perturbation cycle. Women showed higher anterior cruciate ligament antagonistic muscle strength ($p < 0.05$), and lower anterior cruciate ligament activation muscle strength than men. In the standing phase of 57 % -62 %, the peak value of the muscle group of the female quadriceps (QUADs) was about 1.4 times higher than that of the male (± 8.71 N/kg) ($p < 0.05$). Females showed larger gastrocnemius (GAS) peak at two moments: 12.42 ± 4.5 N / kg vs. 8.10 ± 2.83 N / kg, $p < 0.05$ and $2.2 \pm 6, 0.55$ N / kg vs. 0.52 ± 0.09 N / kg, between 95 % and 100 %. On the contrary, the initial posterior tendon peak (HAMS) of males was higher, reaching 10.67 ± 4.15 Newton / kg, while 5.38 ± 1.1 Newton / kg, between 8 % and 11 %. Finally, in males, the peak value of soleus muscle (SOL) almost doubled between 83 % and 92 % in the postural phase, reaching 30.63 ± 8.64 N / kg, while 17.52 ± 3.62 N / kg, $p < 0.001$. These findings suggest that women may exhibit higher risk of neuromuscular control in unexpected situations (such as sports) [7].

2.5 Knee Movement and Landing Action

If the pre-screened female athletes have secondary anterior cruciate ligament injury, they will show a decrease in neuromuscular control and an increase in valgus joint load. In the jump landing task, 205 female athletes participated in high-risk sports related to football, basketball and volleyball through prospective measurement of

three-dimensional kinematics (joint angle) and kinematics. Variance analysis and linear regression and logistic regression were used to isolate the risk predictors of athletes with subsequent anterior cruciate ligament rupture. The results showed that nine athletes were diagnosed with anterior cruciate ligament rupture. The knee posture and weight-bearing of these nine people were significantly different from those of 196 people without anterior cruciate ligament rupture. The knee abduction angle at landing ($P < 0.05$) was 8 degrees higher than that of uninjured athletes. The knee abduction torque ($P < 0.001$) of athletes with anterior cruciate ligament injury was 2.5 times, the ground reaction force ($P < 0.05$) was 20 % higher, and the standing time was shortened by 16 %. Therefore, the increase of motion, force and torque occurs faster. The abduction torque of knee joint predicted the injury state of anterior cruciate ligament, with a specificity of 73 % and a sensitivity of 78 %. Dynamic valgus measurement showed a predicted R^2 of 0.88. Therefore, it can be concluded that knee weight-bearing during knee movement and landing is a predictor of the risk of anterior cruciate ligament injury in female athletes.

3. Prevention of Anterior Cruciate Ligament Injury in Female Athletes

For female athletes, the prevention and control of anterior cruciate ligament injury is always of great significance. Effective prevention programs should systematically incorporate multiple training modules to comprehensively improve neuromuscular control and joint stability. These key training contents include: enhanced, strength, balance, endurance, stability, neuromuscular control, proprioception training, jumping exercises based on concentric contraction, and eccentric training at least three times a week. The above elements do not exist in isolation, but need to be coordinated in the training cycle to form a structured comprehensive intervention system.

The combined use of these programs has been reported to reduce the risk of ACL injury in female athletes by up to 90 % and the overall risk of injury in female football players by about 20 %. Further focus on non-contact ACL injury - this type of injury is particularly prominent in female athletes - through individualized training programs for neuromuscular control, muscle strength, and motor skills, it is expected to prevent up to 65 % of non-contact ACL injury events. These data fully demonstrate that systematic training interventions have a quantifiable and highly clinical value in reducing the incidence of injury [8].

The FIFA 11 + warm-up program designed by the FIFA

Medical Assessment and Research Center (F-MARC) has been widely verified. Studies have confirmed that it can reduce the risk of sports-related injuries for up to one-third of young female athletes. More specifically, the neuromuscular and proprioceptive pre-season training program designed for female athletes aims to train them to avoid knee joints in a 'high-risk position' when landing. Compared with female athletes who did not participate in the prevention program, the risk of anterior cruciate ligament injury can be reduced by 1.83 times. Similarly, Sugimoto et al. showed that structured neuromuscular training programs can reduce the risk of ACL injury in young female athletes [9]. The authors point out that the key elements of the training plan include: more than 20 minutes per training, more than two training sessions per week, ensuring the diversity of training movements, and providing oral feedback [10].

4. Conclusion

The high incidence of anterior cruciate ligament injury in women is due to the synergistic effect of multiple risk factors.

At the anatomical level, the morphological characteristics such as the increase of the posterior slope of the tibial plateau and the reduction of the cross-sectional area of the ligament itself can significantly increase the mechanical stress on the ligament. At the molecular level, estrogen cyclical fluctuations regulate ligament relaxation, and the ovulation period is superimposed with neuromuscular control defects to form a high-risk window, and the up-regulation of ACAN and FMOD genes and the down-regulation of WISP2 suggest that there is gender-dependent regulation of extracellular matrix metabolism.

In terms of biomechanics, women showed greater valgus angle and abduction moment of knee joint in landing and side cutting movements, and the synergistic contraction ratio of quadriceps femoris and hamstring muscle decreased, resulting in weakened dynamic stability of knee joint. During the ovulation period of the menstrual cycle, due to the coexistence of increased ligament relaxation and neuromuscular regulation defects, a high-risk period of anterior cruciate ligament injury is formed.

At the level of preventive intervention, the combined application of structured programs with neuromuscular training as the core (covering enhanced, strength, balance, stability and proprioception training, combined with at least three eccentric exercises per week) can significantly reduce the risk of ACL injury. Among them, the FIFA 11 + warm-up program can reduce the overall risk of sports injury in young female athletes by about one-third, and individualized neuromuscular control training can prevent

up to 65 % of non-contact injuries.

Future research should use machine learning and structural equation model to integrate multi-dimensional data and construct causal prediction maps; using wearable devices and real-time hormone monitoring to achieve dynamic and accurate intervention of menstrual cycle; the molecular mechanism of estrogen regulating ligament remodeling was analyzed by combining single cell multi-omics and organoid model. The universality and compliance of the intervention program were verified by a large sample of long-term randomized controlled trials. Finally, a gender-specific closed-loop management system covering screening, early warning, intervention and rehabilitation was established to provide scientific support for reducing the burden of ACL injury and prolonging the life span of female athletes.

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