The Mechanism of Non-contact Anterior Cruciate Ligament Injury in Female Athletes: Is the Injury Mechanism Different between the Genders?

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Abstract

ACL injury is one of the most frequent and costly injuries in sports, and is a major risk factor for early knee osteoarthritis. Although female gender is a major risk factor for ACL injury, differences in the injury mechanism between males and females have not yet been determined. The goal of this review was to determine whether there is any evidence of gender differences in the mechanisms of ACL injury. MRI studies demonstrated that the location of bone bruises after ACL injury was similar between genders and that males demonstrated more extensive damage in the joint, suggesting the involvement of higher energy but not a difference in injury mechanism. Video analyses of the process of ACL injury has shown common body positions at the time of injury, but failed to reveal differences in the joint motions between genders. Therefore, the mechanism of ACL injury is likely to be similar across genders.

Keywords: Anterior cruciate ligament injury; Non-contact; Mechanism; Risk factor; Gender difference

Introduction

Approximately 75,000 [1-4] to more than 250,000 [5] incidents of anterior cruciate ligament (ACL) tear occur annually in the United States and approximately 200,000 ACL reconstructions are performed annually in the United States [6]. ACL injury is considered one of the most frequent and costly injuries in team sports as well as in military training [7-12] People with ACL injuries are at higher risk for early onset of knee osteoarthritis [13,14], and even successful ACL reconstructions may not prevent early osteoarthritic changes [15-18]. Because short-term outcomes of ACL reconstruction have been proven to be consistent and successful, more attention has recently been directed toward injury prevention [19-26] and the long-term consequences of ACL reconstruction [16-18,27-30].

The risk of an ACL tear is 2-10 times higher in female athletes than in their male counterparts [7,10,11,21,31-36]. Female athletes have 2.4 times higher risk of ACL injury in soccer and 4.1 times higher risk in basketball than male athletes as reported by Arendt and Dick [10] based on the injury reports from the National Collegiate Athletic Association (NCAA). More recently, a meta-analysis by Prodromos et al. demonstrated a female-to-male injury ratio of 2.67 in soccer, 3.5 in basketball [37]. In youth soccer, Lindenfeld et al. [7] reported that 80% of ACL injuries occurred in females, even though female athletes represented only 43% of the total exposure, which is defined as the number of athletes times the total number of practice sessions and games combined. The incidence of ACL injury in elite handball athletes was reported to be 1.6 and 0.23 injuries per 1000 player-hours in female and male athletes, respectively [32], which is similar to the incidence in soccer or basketball [7,8,10]. In a literature review, Hewett et al. [38] estimated that approximately 2,200 ACL injuries occurred annually in female collegiate athletes with a total medical cost of $37 million for all female collegiate athletes and $100 million for female collegiate and high school athletes combined.

Identifying the exact mechanism of ACL injury should play an essential role in establishing efficient and effective prevention programs, by which sports participation for female athletes can be promoted without a higher risk of injury. Risk factor studies have been vigorously conducted in the past decades to understand the general characteristics of high-risk athletes. However, though many studies have shown that ACL injury occurs during a traumatic event in physical activity or sports, the specific joint dynamics that produce a tensile force sufficient to disrupt the ACL has not yet been determined. Moreover, epidemiological and risk factors studies have not identified any gender differences in the ACL injury mechanism that would contribute to a higher risk in female athletes.

Therefore, the objectives of this review article are to: (1) summarise current information on the mechanism of ACL injury, including how risk factors are associated with the injury mechanism; and (2) determine whether there is a gender difference in the mechanism of ACL injury, so that future directions can be proposed for research to clarify the mechanism(s) of ACL injury in each gender.

Risk Factors of ACL Injury

Sports participation

One of the major causes of ACL injury is sport participation, since body contact as well as sudden deceleration of the body seems to increase risk. The characteristics of such situations have been in part described by epidemiological studies.

Nearly 70% of ACL injuries occur during sports participation and the average age at injury is 26 years old [1]. Epidemiological studies in Norway and Sweden showed that ACL injury rates peaked in females in their late teens/early twenties [39-41]. For males, most studies

showed that the peak occurred in their mid to late twenties [39-43] with the exception of one recent study [44]. These data suggest that sports exposure is a risk factor for ACL injury. High-risk sports include basketball [10,11,21,34,45-47], soccer [7,10,11,21,45], gymnastics [36,45,48] and handball [9,19,31,32,49], all of which require abrupt deceleration during landing, cutting and stopping.

There is some evidence indicating how the type of competition affects the risk of ACL injury. An analysis of the NCAA ISS Men's Football Injury Data Set from 2004-2005 to 2008-2009 demonstrated that players are over 10 times more likely to sustain an ACL injury in games than in practices [50]. Data from the NFL's Injury Surveillance System also showed that twice as many ACL injuries occurred during competition compared with those during routine practices [51]. Similarly, Myklebust et al. [19] reported an increased risk of ACL injury during games compared with that during practice in the Norwegian Handball League. A plausible explanation for this significant trend is that game conditions involve a less predictable playing environment as well as greater speeds and intensity. The level and type of competition may influence the risk of ACL injury.

Several studies showed that approximately 70% of all ACL injuries occur in non-contact situations [10,32,36,49,52,53]. Based on their questionnaire survey, Boden et al. [52] reported that 71% of injuries occurred in non-contact situations. In handball, nearly all of the injuries occurred in non-contact situations [32]. Even in collision sports, such as Australian football [54], there was a higher rate of non-contact ACL injuries over contact injuries. Exceptions to this tendency were found in collision sports such as American football [51] and rugby [42,55] in which more direct contact mechanisms were involved. Overall, the rate of non-contact ACL injury is approximated to comprise 70% of all ACL injuries [20,52]. In the non-contact mechanism in sports, sudden deceleration during landing, cutting and stopping is the movement most likely to result in ACL injury to athletes of both genders. These movements require muscle power, quick reversal activities between agonist and antagonist muscle groups, high velocity eccentric muscle activity and stabilization of joints against large ground reaction force. Details of these movements are described in subsequent sections.

Hormonal cycle and ligamentous laxity

Hormonal cycle in females has been considered a possible risk factor for ACL injury, since the existence of sex hormone receptors in the human ACL has been reported [56-59]. Females generally have greater ligamentous laxity than males [60] and the female ligamentous laxity is modified by hormonal activities. The menstrual cycle is divided into three phases: follicular (days 1 through 9, low progesterone and oestrogen), ovulatory (days 10 through 14, preceded by an oestrogen surge), and luteal (days 15 through 28, rise in progesterone and a later rise in relaxin) [61].

An animal study in rats showed that a ligament's collagen content and fibril diameter are considerably increased by ovariectomy and significantly decreased by the administration of oestrogen alone or oestrogen combined with progesterone [62]. Shikata et al. [63] found that oestrogen significantly decreased the collagen content in the cellular matrix in the rat hip joint capsule and increased the elastin content. Furthermore, oestrogen enhanced the effects of relaxin [64], which increases the rate of remodelling and makes ligaments weaker in rats [65]. Specifically, relaxin enhanced the remodelling activity of the connective tissues of the pubic symphysis in pregnant female mice [66]. Therefore, it is suspected that oestrogen increase during the

hormonal cycle increases the elasticity and decreases the tensile strength of the ACL, which may increase the risk of ACL injury. Furthermore, combined administration of oestrogen and cyclic loading in pigs inhibited the mRNA expressions of collagen I, III and biglycan, whereas either oestrogen administration or cyclic loading alone increased the gene expression of only collagen I or collagen I and III, respectively [67]. Recent evidence showed that elite female athletes with ACL injury have higher serum relaxin concentration (SRC) than those without ACL tears; those with an SRC greater than 6.0 pg/mL showed over 4-fold increased risk of ACL tear [68]. Accordingly, results from these studies support a hypothesis that an increase in female hormones can be a risk factor of ACL injury.

As for the association between the hormonal cycle and ACL injury, females appear to be at higher risk during the ovulatory phase or the follicular phase (Figure 1) [19,33,53,69-74]. The consistency of this finding is interesting and may indicate that there is a difference between the first and second halves of the menstrual cycle, with more injuries occurring in the preovulatory phase. The observed association between menstrual cycle and ACL injury risk indicates that there are effects of hormonal fluctuation on either passive or dynamic knee stability. Findings of studies on the effects of the menstrual cycle on knee joint laxity are summarized in Figure 1. Five of the eleven studies observed significant associations between the menstrual cycle and anterior knee laxity and all five reported that laxity increased during the ovulatory or luteal phases of the cycle [75-80]. Furthermore, a meta-analysis of nine studies found that anterior knee laxity was greater in the ovulatory phase than in the luteal phase and was lowest in the follicular phase [81]. This is inconsistent with the injury data, which are more indicative of injuries occurring during the first half of the cycle, when the ACL (or knee) would be less lax or demonstrate greater stiffness. Therefore, the association between the menstrual cycle and injury may not be the same as the relationship between the menstrual cycle and knee laxity.

In humans, it is not easy to determine whether ligamentous laxity is truly influenced by the hormonal cycle due to several limitations. First, arthrometric testing for ACL laxity in vivo involves a standard deviation of more than 2 mm in healthy knees and more than 3 mm in ACL-deficient knees [1,82-84], whereas the change in anterior-posterior laxity between the follicular and ovulatory phases was only 0.26 mm (4.98 and 5.24 mm, respectively) [85]. Second, there is difficulty in controlling the testing schedule with regard to the hormonal cycles of each subject, so that maximal changes in the ACL strain during the hormonal cycle may not have been detected. Third, normalization of the elongation distance by arthrometric testing in relation to another body part (e.g. ACL length, tibial width or height) would be necessary to compare the laxity changes across individuals, which generally has been discarded in past studies since exact measurement of ACL length requires detailed 3-dimensional reconstruction of the knee anatomy. For example, Belanger et al. tested the effects of exercise and hormonal cycle on ACL laxity using a KT-2000 arthrometer with an anterior force of 134N in 27 female athletes [86], and found that there were no significant differences in anterior laxity among the follicular, ovulatory, and luteal phases of the menstrual cycle or between pre- and post-exercise conditions.

The menstrual cycle may affect active restraints (neuromuscular in nature) rather than passive restraints (ligament) of knee stability, because the menstrual cycle affects motor control and muscle strength [87,88]. Warden et al. [89] reported that oestrogen and its receptors in fact do not affect ACL mechanical properties, and suggested that more

emphasis be placed on investigation of neuromuscular factors that may be related to increased ACL injuries in female athletes. However, there is little evidence to support this hypothesis. Hertel et al. [90] reported an absence of significant differences in measures of strength, joint position sense, postural control, or laxity across the menstrual cycle despite varying oestrogen and progesterone levels. Chaudhari et al. [91] also found that there were no significant differences in moments or knee angle among phases of the menstrual cycle. On the other hand, Cesar et al. [92] observed significantly smaller knee valgus angles during the luteal phase compared to those during the other two phases.

Despite supporting data from basic science studies, outcomes of in vivo studies to date have been inconsistent or less reliable due to several limitations such as small sample size or less accurate measurements. More rigorous study is needed to determine the effects of hormonal cycle on the risk of ACL injury.

Anatomical factors within the knee joint

Gender differences in anatomical characteristics have been implicated in ACL injury and a smaller intercondylar notch width of the femur in females has been considered a candidate risk factor for ACL injury. In a study of 46 female handball players (20 players with ACL injury, 26 controls), the individuals with 17 mm or less anterior notch width were 6 times more susceptible to ACL injury compared to players with a greater notch width [93]. Comparing notch width between knees with acute ACL tear (n=63) and normal knees (n=38), the ACL tear group showed a significantly narrower anterior notch width on anteroposterior radiography [94]. Analysing the 3-dimensional shape of the notch, Anderson et al. [95] suggested that narrowing at 2/3 of the notch height, where 0/3 is defined as the distal outlet and 3/3 the deepest point of the notch, was associated with a higher occurrence of ACL injury. Another 3-dimensional analysis of the morphology of the knee indicated that a narrower posterior notch width might predispose a knee to an ACL tear [96].

Several larger cohort studies have been published regarding the relationship between notch width and risk of ACL injury. During a 2-year follow-up period involving a cohort of 902 high school athletes, 3% of the subjects sustained ACL injury and athletes with a stenotic notch were determined to be at significantly greater risk [97]. Risk factors for ACL injury in 859 new United States Military Academy cadets (739 men, 120 women) were studied by Uhorchak et al. [98]. Twenty-four ACL non-contact tears (16 in men, 8 in women) occurred during the study period, and the risk factors were determined to be: 1) radiographic indices of the notch width and ACL size as well as generalized joint laxity for both genders; and 2) higher BMI and increased knee laxity for females. More importantly, subjects with more than one of these risk factors were at much greater risk than those with one risk factor or none at all. Non-contact ACL injuries occurred in all women demonstrating a combination of narrow femoral notch (≤13 mm), BMI that was 1 SD or more above the mean, and either generalized joint laxity or sustained KT-2000 arthrometric values that were 1 SD or more above the mean [98].

Caution is needed when attempting to draw an accurate conclusion from studies associated with notch width. Females have a narrower notch width than males in both adolescent and general adult populations [97,99], while females generally have a smaller notch width as well as smaller femoral condylar width as compared to men [99,100]. Therefore, a notch index (the notch width divided by the femoral condylar width) should not be used as an indicator of the risk

factor across genders. Moreover, the notch width increases with height in males, but not in females, therefore normalization of the notch width to the height of the athletes is inadequate when inter-gender comparison is intended [100].

Shelbourne et al. [99] suggested that it may be the absolute size of the ACL that predisposes people with narrow femoral notches to ACL injuries rather than the notch width itself [99]. This suggests that a smaller ACL is more susceptible to injury because it supposedly has weaker tensile strength. However, the notch width may not be an indicator of ACL size, since notch width failed to predict the ACL size in a Japanese population as reported by Muneta et al. [101] Accuracy of measurement is another issue in which caution is needed. Arendt [102] pointed out that a 2-dimensional measurement of the notch width using radiography was likely to include uncontrolled rotational and flexion alignment of the knee, and that the size of the ACL was difficult to define because of the irregular cross sectional morphology and shape changes with the knee angle.

The biomechanical rationale of the smaller notch or smaller ACL cross section has not yet been determined. One clear explanation was proposed in a hypothesis by Shelbourne et al. [99] that a smaller ACL, which is supposedly weaker, is a direct risk factor for female ACL injury. Another hypothesis by Olsen et al. [49] suggested that the ACL is impinged by the lateral femoral condyle at the anterior outlet of the notch during tibial external rotation under quadriceps force. To prove this theory, the engaging mechanism of the ACL and the anterior notch would need to be identified in which factors including cross section of the ACL, notch width, shape of the anterior outlet of the notch as well as rotational alignment of the knee would be precursors. To further analyse this mechanism, it would be necessary to obtain direct in vitro measurement of ACL strain and the contact pressure between the ACL and the lateral femoral condyle under combined muscle loads.

Other anatomical factors have also been proposed recently. A study of patients with bilateral ACL injuries demonstrated that the injured group had significantly wider lateral femoral condyles than controls and the incidence was significantly higher in individuals with a family history of ACL injury [103], suggesting that anatomical factors are involved. Although no biomechanical rationale was suggested in this study, a wider lateral femoral condyle may produce a longer moment arm from a valgus force applied to the knee, resulting in a greater torque or moment inducing a valgus collapse of the knee.

A larger posterior-inferior slope has been proposed as a factor that increases the tensile stress of the ACL. Griffin et al. [104] showed that knees with a large caudal slope of the tibial plateau demonstrated increased anterior translation of the tibia. During a single-legged land-and-cut task, McLean et al. [105] reported a strong association between lower medial:lateral TPS ratios (lateral > medial) and greater peak knee valgus and internal rotation of the tibia relative to the femur. Furthermore, greater lateral TPS was associated with greater anterior joint reaction force. These findings suggest that the ACL was more stretched or tensioned due to posterior glide of the femoral condyles on the tilted tibial plateau. Hashemi et al. [106] found that females with ACL injury had an increased posterior-inferior-directed lateral tibial plateau slope (TPS) and shallower medial tibial plateau depth (TPD) compared with uninjured controls. Males with ACL injury had an increased posterior-inferior-directed medial and lateral TPS and shallower medial TPD compared with uninjured controls. Khan et al. [107] confirmed this finding in female patients. However,

one small clinical study found that there was no difference in the caudal slope between ACL-injured knees and a control group [108].

Overall, there is some agreement regarding an association between the absolute notch width and an increased risk of ACL injury, and further research is needed to determine how the notch engages with the ACL at the time of injury. Although such a study is expected to contribute to determining the specific injury mechanism, measurement accuracy and appropriate normalization in discussing the anatomical factors is a significant concern and more accurate 3-dimensional analysis will be required to clarify the contribution of each anatomical factor proposed. Other anatomical factors including the posterior-inferior slope of the tibia need to be investigated in a larger study.

Skeletal alignment

Factors associated with skeletal alignment, such as physiological valgus and the Q angle of the knee extensor mechanism may also be linked to ACL injuries. Females have been reported to have a larger physiological valgus of the knee, which is caused by female anatomical characteristics including a wider pelvis, larger femoral anteversion, larger physiological valgus and larger Q-angle [35]. However, one study showed that females have a larger Q-angle due to a shorter femur rather than wider pelvis, while males have a larger absolute width of the pelvis [109]. Yoshioka et al. [110] reported that females have a smaller femoral condylar width, femoral head, and antero-posterior dimension of the femoral condyle, but no difference in femoral anteversion.

The association between skeletal alignment and ACL injury is unclear. The relationship between the Q-angle and ACL injury was studied by Gray et al. [111], but there was no association found. Huegel and Meister [112] reported, in a small study, that the Q-angle did not show any association with ACL injury, but the larger thigh-foot angle (larger valgus at the knee joint combined with greater pronation at the subtalar joint) was associated with increased ACL injury. Therefore, there has not been sufficient research into the possible association between static skeletal alignment and the risk of ACL injury and importantly, there are no studies that included all possible or sequentially additive skeletal malalignment factors that have been linked to the risk of ACL injury. Since skeletal alignment demonstrates clear gender differences, future studies should include 3-dimensional anatomical analyses of the entire lower extremity in order to identify any possible association between skeletal alignment and the risk of ACL injury.

Neuromuscular factors

The role of neuromuscular control including the timing of muscle activation, muscle stiffness, awareness of joint positions, and balance and proprioceptive function have been studied in relation to the risk of ACL injury in female athletes. There is some evidence showing that neuromuscular training reduces the risk of ACL injury [19,20,38,61,113-123].

As demonstrated by in vitro biomechanical simulation studies, knee motion produced by knee joint muscle activation affects ACL strain. Anterior translation of the tibia during knee extension utilizing simulated quadriceps force has been measured during open chain isometric knee extension. Anterior translation of the tibia during simulated isometric quadriceps contraction generally occurs between 75^0 of knee flexion and 0^0 [124-127], while posterior translation of the tibia occurred between 80^0 and 120^0 [126]. The significance of the quadriceps force on the native ACL was tested by DeMorat et al. [128].   Simulated isometric knee extension with 4500N of isolated quadriceps force caused irreversible ACL elongation in 6 of 13 human cadaveric knee specimens, suggesting that isolated quadriceps force alone can damage the ACL. Utilizing a robot/universal force sensor system to measure the in situ forces of the ACL as well as anterior displacement of the tibia under isolated quadriceps force or combined quadriceps and hamstring forces, the effect of adding hamstring force was determined by Li et al. [129]. Added hamstring force reduced the anterior translation of the tibia and in situ force of the ACL in knee flexion greater than 30^0, whereas it had a limited effect on reducing the anterior translation when the knee flexion was less than 30^0. Accordingly, in vitro studies agree that isolated quadriceps force, i.e. without hamstrings activation, should be treated as a major risk factor of ACL injury. Although activation of the hamstring may protect the ACL when the knee is in flexion, it may have no or only limited effect in extension (i.e. <30^0) [129]. Interpretation of these results would require further consideration of hip and trunk positions, since the muscle activation pattern around the knee is significantly influenced by the body position.

Most non-contact ACL injuries appear to occur shortly after foot plant during cutting, stopping or landing with the knee slightly flexed and closed kinetic conditions should be discussed to determine the effects of muscle activation patterns on ACL strain [49,52]. Posterior positioning of the body, i.e. posterior positioning of the centre of mass, during deceleration in closed kinetic chain was found to be a risk factor for ACL injury [52], although the level of this evidence should be considered weak due to the small sample size. Major differences between the closed and open kinetic chain conditions include the level of joint loading and muscle activation patterns, in which the hamstrings and gastrocnemius are usually active in addition to the quadriceps in closed kinetic chain activities [130]. In landing, the biceps femoris and gastrocnemius were shown to be active shortly before foot contact and prior to the activation of the quadriceps [131], and the authors concluded that this knee flexor activity would decrease the resultant anterior shear force of the tibia at landing. The question remains as to how effective knee flexor activity is in preventing ACL injury and if it is very effective, how can these muscles be activated as an effective sport strategy.

The hamstrings, strong antagonists of the quadriceps at the knee joint, are generally thought to reduce strain on the ACL in the closed kinetic chain condition. The hamstrings usually are active in closed kinetic chain activities, because the hip extensors, including the hamstrings, are antigravity muscles at the hip and function with the quadriceps, the antigravity muscles at the knee. Squatting exercise with load in addition to body weight generated approximately twice as much hamstring activity on EMG as leg press or open kinetic chain knee extension [132,133]. During squatting exercise, peak hamstring activity was observed between approximately 30% and 80% of the Maximal Voluntary Contraction (MVC) occurring near 50°–70° of knee flexion. In contrast, minimal EMG activity of the hamstring muscles between 12% and 20% MVC occurred during squatting exercise with body weight load only [133-135]. The level of hamstring activation during squatting may be dependent on body postures or positions and ACL injury may occur at landing, cutting or stopping when hamstring activation is reduced due to the specific body position. For example, squatting exercise in healthy subjects with the body leaning anteriorly against a wall (anterior body position) produced less quadriceps and hamstrings activity and more

gastrocnemius activity as compared with squatting exercises with the centre of mass in an over-the-foot position (neutral) or with the body leaning posteriorly against the wall (posterior body position) [136]. This study also showed that anterior translation of the tibia during squatting in ACL-deficient knees was largest in the anterior body position and smallest in the posterior body position, suggesting that decreased hamstring activation in the anterior body position might contribute to larger anterior translation of the tibia [136].

A computational model predicted that the ACL was loaded only in the first 25% of landing with peak ACL force equalling 40% of body weight, at which time the ankle was in dorsiflexion and the hip was in slight flexion so that the shank and trunk aligned nearly parallel in the sagittal plane [137]. Results of the in vitro study by Li et al. [129] suggested that hamstring force did not effectively unload the ACL when the knee was in extension (i.e. <300 of knee flexion). Accordingly, hamstring force may be neither efficient nor effective in preventing ACL injury during the high-risk phase of landing because the knee is typically flexed only 10-150 at foot contact. Improved neuromuscular training to promote hamstring activation at landing by establishing a good landing position with deeper knee flexion [138-141] would promote co-contraction of the quadriceps and hamstrings.

Although the gastrocnemius is a knee flexor, its role in anteroposterior stabilization of the tibiofemoral joint is not clearly understood. Moderate gastrocnemius activity during the squat was reported by Escamilla et al. [132], who showed that EMG activity progressively increased as the knees flexed and decreased as the knees extended. This is reasonable because as the knees flex, the ankles become dorsiflexed, resulting in greater dorsiflexion demand moment or torque and therefore more gastrocnemius activity with knee flexion. Peak gastrocnemius activity occurred between 600 and 900 of knee flexion during squatting with the ankle joints in slight dorsiflexion and the heels on the floor, which also produced a large dorsiflexion demand moment [132,133]. Kvist and Gillquist [142] measured anterior translation of the tibia and EMG activity of the leg muscles during stair descending in ACL-deficient knees. For the weight-bearing lower limb, the greatest gastrocnemius activity reached only 30% of MVC at the mid-point of the stance phase when the knee flexion angle was at 850 and the ankle was assumed to be near maximal dorsiflexion, whereas it was less than 15% MVC when the knee flexion was less than 450. Therefore, the gastrocnemius is relatively active in a squatting position when the centre of mass is located posteriorly and the ankle is dorsiflexed. However, it is not as active while descending stairs when the centre of mass is located anteriorly and the dorsiflexion demand moment is supposedly small. Furthermore, considering that the gastrocnemius activity reaches its maximum between 600 and 900 of knee flexion, it may not be efficient in preventing ACL injury in the high-risk position during the initial phase of landing when the knee is only slightly flexed. Its activity would be further minimized if the vector of the centre of mass during deceleration were parallel to the mechanical axis of the tibia, because the dorsiflexion demand moment is assumed to be zero under that condition.

Hamstring and gastrocnemius muscle activities during landing, cutting or stopping may reduce ACL load judging from their line of action, but the positions of the hip and ankle/subtalar joints as well as the loading balance between the heel and forefoot are major determinants of muscle activity. If the centre of mass were located at a posterior position during deceleration, the heel would be more likely

be planted flat on the ground with the ankle plantarflexed, with less dorsiflexion demand moment, so that a large decelerating force would be generated with less quadriceps contraction. If the knee and hip were in slight flexion, the activity of the gastrocnemius would be reduced. On the other hand, if the landing was intentionally made in a deeper squatting position, muscle activity of the hamstrings and gastrocnemius might be enhanced according to the findings on EMG studies [132,136]. Here, strategic neuromuscular control and the contributions of training programs might contribute to optimizing muscle activity patterns in order to reduce the mechanical load on the ACL [25,138].

In summary, specific muscle activation patterns along with the specific joint and body positions may contribute to non-contact ACL injury. A number of variables must be clarified before a specific biomechanical model of ACL injury can be created and validated. Measurement of ACL strain in vivo in various knee positions, while obtaining EMG activity of the leg muscles and 3-dimensional knee kinematics, would be valuable. A technique for ACL strain measurement has been established by Beynnon and co-workers [143-149] and will be described in a subsequent section.

Effects of neuromuscular training

Effective neuromuscular training programs may decrease the risk of ACL injury. Griffis et al. reported an 89% reduction in the risk of injury over a 10-year period in female collegiate basketball players [150]. These authors trained athletes to perform a flexed-knee landing instead of a straight-knee landing and a flexed-knee 3-step stop instead of a one-step stop. In Italy, Caraffa et al. [113] used proprioceptive training to emphasize balance improvement for 20 minutes per day in 5 different phases for 600 soccer players. There was an 87% reduction (RR 0.13, p<0.001) in the incidence of ACL injury in the training group in comparison to that in the control group. In Norway, Myklebust et al. [19] studied the effectiveness of neuromuscular training, emphasizing awareness of the knee position and maintenance of an over-the-toe knee position (the knee is over the toe in the frontal view) during handball. This program was applied to over 800 elite female handball players, who were under the supervision of physical therapists, and ACL injuries decreased from 29 in 942 players during the first intervention season to 17 in 852 players during the second intervention season. In 2011, LaBella et al. [151] studied the effects of a neuromuscular warm-up program on ACL injury rates in female high school athletes in Chicago public schools. The warm-up involved plyometrics, balance, progressive strengthening and agility exercises as well as instruction on how to avoid dynamic knee valgus and how to land after a jump with flexed hips and knees. At the end of the season, the ACL injury rate was significantly lower in the intervention group compared with that in the control group. This program is known as KIPP, Knee Injury Prevention Program.

Negative results have also been reported. Soderman et al. [115] found no difference in the incidence of ACL injury in their underpowered prospective, randomized study evaluating female soccer players. In addition to the small number of athletes, their only intervention was balance board training for a period of ten to fifteen minutes during the season. Heidt et al. [152] included 42 female soccer players into their Frappier Acceleration Training Program and compared them with 258 controls. A 7-week training program, including cardiovascular conditioning, strengthening, and flexibility and plyometric exercises, was established in the intervention group. They observed nine ACL injuries over a period of 1 year, and eight of

these injuries occurred in the control group. Petersen et al. [118] studied the effects of a prevention program on the incidence of injury in female German team handball players over the course of one season. The program focused on balance and jump training and the athletes were analysed and given feedback regarding technique and landing positions. There were five ACL injuries in the control group (all noncontact), and one (contact) in the intervention group. The odds ratio was 0.17; however, the Confidence Interval (CI) was 0.02 to 1.5 as this was an underpowered study. Pfeiffer et al. [117] examined the effectiveness of a Knee Ligament Injury Prevention (KLIP) program. The drills in the KLIP program consisted of running, jumping, and landing in forward and backward directions; the athlete initially landed on both feet and later progressed to landing on a single foot. They observed no significant difference in the rate of knee injuries between the groups, and concluded that the rate of non-contact ACL tears would not be lowered by use of the KLIP program. Finally, Steffen et al. [153] found no significant decrease in a cluster-randomized controlled trial examining female youth soccer players and a set of exercises known as the "11". While the design of the study was good, the compliance in the intervention group was only 24%.

In the U.S., a series of studies has been published by Hewett and co-workers from Cincinnati Children's Hospital [38,154-156], who used a training program consisting of flexibility training, strength training for the trunk and lower extremity as well as jump (plyometric) training for female athletes under the supervision of athletic trainers or physical therapists [154]. The plyometric training emphasized balance and proper landing techniques of maintaining an over-the-toe knee position and reducing landing forces (soft landing technique). This plyometric training decreased an average of 50% of abduction and adduction knee moments during landing as measured by a motion capture system with force plates, and resulted in increasing the hamstring-to-quadricep strength ratio as measured by an isokinetic testing device [154]. Moreover, their prospective non-randomized cohort study involving 1263 female high school athletes demonstrated a significant reduction in the incidence of ACL injury from 0.43 in 1000 athlete-exposures to 0.12, whereas the incidence for untrained male athletes was 0.09 [38]. A gender difference in the landing technique prior to training was later reported by Ford et al. [155]. Female high school athletes landed with greater total valgus knee motion (female: 7.3 ± 0.5 cm, male: 5.3 ± 0.5 cm, p=0.005), greater normalized valgus knee motion to height (female: 0.043 ± 0.003 cm/height, male: 0.029 ± 0.003 cm/height, p=0.001) and a greater maximum valgus knee angle than male athletes (female: 27.6 ± 2.2°, male: 16.1 ± 2.2°, p<0.001). Moreover, female athletes showed significant differences in maximum valgus knee angle between their dominant and non-dominant sides. Myer et al. [157] compared the effects of a neuromuscular training program between high-risk and low-risk subjects. Based on data from previous research [158], high-risk and low-risk groups were identified through motion analysis of a drop vertical jump and calculation of knee abduction moments. Athletes classified as high-risk significantly decreased their knee abduction moments by 13% following training. Athletes grouped into the low-risk category demonstrated hardly any change into their abduction moments following training. These results indicated that "high-risk" female athletes decreased the magnitude of the previously identified risk factor for non-contact ACL injury following neuromuscular training. Unfortunately, the mean values for the high-risk subjects were not reduced to levels similar to those in the low-risk group following training. Targeting female athletes who demonstrate high-risk knee abduction loads during dynamic tasks may show

improved efficacy following neuromuscular training. It was suggested that increased training volume or more specific techniques might be necessary for high-risk athletes to substantially decrease their non-contact ACL injury risk. Interestingly, the valgus knee motion at landing was identical between boys and girls at the pre- and early pubertal phase, whereas girls demonstrated a significantly larger valgus motion (normalized by height) (p<0.01) at the late- or post-pubertal phase [159]. There was also a smaller knee flexor torque normalized by body weight compared with that shown by the boys (p<0.01) [159]. Although girls tend not to develop increased leg strength during puberty, placing them at higher risk for ACL injury after maturation, this deficit can be minimized by a properly designed strengthening and neuromuscular training program [38,154].

Based on the above studies, Hewett et al. [155,160] summarized the 3 components of neuromuscular imbalance, including ligament dominance, quadriceps dominance and leg dominance, which would increase the risk of ACL injury. Ligament dominance is characterized by an increased dependency on the knee ligaments to absorb the ground reaction force rather than utilizing lower extremity muscle activation. This often results in increased valgus motion at landing in female athletes. Quadriceps dominance is defined as a greater than normal recruitment of the quadriceps over the hamstrings due to an imbalance between quadriceps and hamstring strength. This dominance may increase the anterior shear of the tibia at landing. Lastly, leg dominance indicates an imbalance between muscular strength and coordination in opposite limbs, with the dominant limb usually demonstrating greater strength and coordination. This causes a larger ground reaction force in the dominant lower limb, placing the dominant knee at higher risk for ACL injury.

In a non-randomized study, Mandelbaum et al. [61] studied the effects of implementing the PEP program (Prevent Injury and Enhance Performance Program) in a large group of female club soccer players. The intervention was a 20-minute exercise regimen performed 2-3 times a week during the 12-weeks season. The intervention athletes watched an educational video on safe and unsafe landing patterns, and participated in team workouts of stretching, strengthening, plyometrics, and soccer-specific agility drills, which replaced the team's warm-up during soccer practice. There was a heavy emphasis on proper technique: landing technique, stressing "soft landing" and deep hip and knee flexion as opposed to landing with a "flat foot" in lower extremity extension. This resulted in an 88% and 74% overall reduction in ACL injury rates in the intervention group during the first and second year, respectively. Three years later, the same group studied the effect of the PEP program on NCAA division 1 women's soccer teams in a randomized controlled trial [121]. There were lower rates of total and noncontact ACL injuries in the intervention group but the difference was not significant. However, when the results were evaluated for the second half of the season, weeks 6-11, there were significantly lower rates of total ACL injury in the intervention group. The fact that significant differences in the injury rates were seen only in the second half of the study suggests that the program takes some time to have an effect, thus arguing for implementing ACL prevention programs earlier, prior to the season start, in order to have an effect on ACL injury rates during the season. Finally, Lim et al. [161] investigated the effects of a modified PEP program on biomechanical properties associated with ACL injury in female basketball players. A comparison of the groups after training demonstrated that the experimental group had significantly higher maximum knee flexion angles, greater knee distances, lower

hamstring-quadriceps ratios, lower maximum knee extension torques, and higher maximum knee valgus moment than the control group.

Neuromuscular training, including balance and jump training, appears to improve the neuromuscular control of the knee joint and knee biomechanics during landing, which would likely decrease the risk of ACL injury in females. Considering the published evidence supporting the effectiveness of neuromuscular training programs, it is hypothesized that valgus knee motion and/or moment at landing may be a major risk factor for ACL injury. However, the neuromuscular factor may not be the only factor contributing to valgus motion. Some anatomical factors, such as relatively shorter femur, excessive femoral anteversion, excessive lateral tibial torsion, as well as hypoplasia of the lateral posterior femoral condyle, may contribute to the excessive valgus motion in females. Therefore, it would be beneficial to determine the relative contributions of anatomical and neuromuscular factors to the occurrence of the valgus motion at landing in prospective studies. Furthermore, it is unclear if excessive valgus force increases the load on the ACL and causes ligament rupture, because excessive valgus knee motion is seen in athletes much more commonly than ACL injury itself. Thus, clarifying the contribution of each risk factor to ACL loading and to ACL injury would provide valuable information.

Determination of the Injury Mechanism

Questionnaire surveys and video analyses

Notation of specific body positions at the time of ACL injury, questionnaire surveys and video analyses have been conducted in an attempt to determine ACL injury mechanism. In 1999, the American Academy of Orthopaedic Surgeons published a comprehensive review entitled "Prevention of non-contact ACL injuries". Myklebust et al. [31,32] conducted a questionnaire survey of ACL injuries in handball players and found that nearly all the injuries (n=25) occurred in non-contact situations when the players performed high-speed plant-and-cut movements.

Systematic video analysis of injuries can potentially contribute information on athlete movement patterns that lead to ACL injury. Teitz [162] used a multi-centre video analysis technique to study 14 basketball injuries. In this study, all male players injured their ACLs at landing, whereas about half of the female players were injured while stopping with the centre of mass posteriorly placed while the upper body leaned backward. Olsen et al. [49] reported a video analysis focused on the ACL injury mechanism in elite female handball players in Norway using videotapes of 20 ACL injuries occurring between 1988 and 2000. These injuries consisted of 19 non-contact mechanisms and most of the injuries resulted from a plant-and-cut faking movement or one-leg landing after a jump shot in which the knee was close to full extension combined with internal or external rotation of the tibia, followed by a forceful valgus collapse occurring in a non-contact manner. Experienced coaches reviewed the videotapes and concluded that most of the injured athletes appeared to experience disturbed balance with or without body contact prior to the injury. Boden et al. [52] reported a combined video analysis and questionnaire survey involving 89 injured athletes (100 knees) who were asked about events surrounding the ACL injuries. The questionnaire survey for these 100 knees indicated that in seventy-two knees (72%), injuries were classified as due to non-contact mechanisms. Video analysis for 27 of 100 knees showed that 15 of the injuries were sustained due to a non-contact mechanism including

sudden deceleration and change of direction at landing. ACL injury was supposed to have occurred prior to valgus collapse at foot strike with the knee close to full extension, but no further information was reported. Krosshaug et al. [163] performed visual inspection analyses of 39 videos of ACL injury situations. They found that valgus knee collapse was a common ACL injury mechanism with female basketball players demonstrating a 5.3-fold higher relative risk of abduction collapse during ACL injury compared with that of male basketball players. Hewett et al. [164] analysed still captures from 17 injury videos (10 female and 7 male players with ACL injuries or 6 videos of female controls performing similar landing and cutting tasks. They reported female subjects with ACL injuries showed greater lateral trunk angles and greater knee abduction angles during ACL injury compared with those of female control athletes and male subjects during similar landing and cutting tasks. Boden et al. [165] also conducted a similar case-control study of one-limb landing positions associated with ACL injury and non-injury. They found that injury occurred when the foot was less plantar flexed and the hip was more flexed during landing. On the basis of these findings, the so-called provocative landing position was defined as the tibial slope relative to the femur being in a more inferior to superior direction than that in the safe position [166].

Although video analysis is the only method available to extract kinematic data from actual injury situations to clarify the mechanisms for noncontact ACL injury, it is often pointed out that most studies have been limited to simple visual inspection, the accuracy of which has been shown to be limited. Recently, as an alternative, a model-based image-matching (MBIM) technique has been developed to extract joint kinematics from uncalibrated video recordings [167,168]. This technique has been validated in noninjury situations in a laboratory environment and has also been found to be feasible for use in actual ACL injury situations. Using this method, Koga et al. [169] analysed 10 ACL injury video sequences from women's handball and basketball. The mean knee flexion angle among the 10 cases was 23° at Initial Contact (IC) and had increased by 24° within the following 40 milliseconds. The mean valgus angle was neutral at IC, but had increased by 12° 40 milliseconds later. The knee was externally rotated 5° at IC, but rotated internally by 8° during the first 40 milliseconds, followed by external rotation of 17°. The mean peak vertical ground-reaction force was 3.2 times body weight and occurred at 40 milliseconds after IC. Based on when the sudden changes in joint angular motion and the peak vertical ground-reaction force occurred, it is likely that anterior cruciate ligament injury occurred within 40 milliseconds after IC. The kinematic patterns were surprisingly consistent among the 10 cases. All players demonstrated immediate valgus motion within 40 milliseconds after IC. Moreover, the tibia rotated internally during the first 40 milliseconds and then external rotation was observed, possibly after the ACL had torn. These findings suggest that valgus loading is a contributing factor in the anterior cruciate ligament injury mechanism and that internal tibial rotation is coupled with valgus motion. A similar result was described in a subsequent case report of a male soccer player [170].

In 2010, Koga et al. [169] combined his current study with previous findings to propose the following hypothesis for the mechanism of noncontact ACL injury. (1) When valgus loading is applied, the medial collateral ligament becomes taut and lateral compression occurs. (2) This compressive load, as well as the anterior force vector caused by quadriceps contraction, causes displacement of the femur relative to the tibia where the lateral femoral condyle shifts posteriorly and the tibia translates anteriorly and rotates internally, resulting in ACL

rupture. (3) After the ACL is torn, the primary restraint to anterior translation of the tibia is gone. This causes the medial femoral condyle also to be displaced posteriorly, resulting in external rotation of the tibia. This external rotation may be exacerbated by the typical movement pattern when athletes plant and cut, where the foot typically rotates externally relative to the trunk.

Interpretation of video analyses and questionnaire surveys were consistent in demonstrating that the majority of ACL injuries occur in non-contact situations and the athletes hear a "pop" approximately 30 to 40 milliseconds after foot strike during sudden stopping, cutting or landing, which they routinely use. The knee position at the moment of injury is in slight flexion and valgus with the tibia internally rotated, followed by a sudden valgus collapse. Whether there are gender differences in the knee position remains uncertain due to inconsistent findings [49,52,171]. Although a decelerating motion typically requires well-controlled eccentric knee flexion for shock absorption after foot plant, this cushioning action was lacking in injured athletes at landing as sudden valgus collapse occurred. A possible reason for this is a restriction of range of motion of hip joint. Recently, the mechanics of the hip, especially a restricted passive range of internal rotation at the hip, has been correlated with ACL injury and reinjury in soccer players [171,172]. Beaulieu et al. [173] evaluated the impact of decreased internal femoral rotation on peak ACL strain during simulated single-leg pivot landing and found they were inversely related. A decelerating motion that develops a large tibial internal rotation torque result in particularly high-peak ACL strain [174]. Therefore a deficiency in hip internal rotation may result in compensatory increases in stresses applied to the ACL, thereby increasing the risk of ACL injury.

Limitations in video imaging at present include the small image size of the injured athletes within the camera frame, interruption in visualizing the athlete's knee, and the sampling rate of the video camera. Multi-directional high-speed video cameras are necessary to obtain specific knee position or a sequence of knee motions at the time of injury for a substantial number of subjects. Limitation also includes the difficulty in measuring frontal- or horizontal-plane knee motion, as these are very small in comparison to sagittal plane motions.

MRI analyses

Impact injury of the femur on the tibial plateau during ACL injuries result in bone bruises. The presence of bone bruises was first described by Mink et al. [175] after reviewing MRI of the knee associated with medial collateral ligament (MCL) injuries. Mink et al. [176] later reported that bone bruises in the lateral femoral condyle and/or lateral tibial plateau were observed in 72% of ACL injured knees, and this finding has been confirmed by other researchers [177-187]. Histological changes in the articular cartilage overlying a geographic bone bruise demonstrated significant injury to the homeostasis of the articular cartilage over the bone [183]. Single photon emission computed tomography (SPECT), a 3-dimensional bone scan, for acute ACL injury demonstrated a "kissing" pattern of increased uptake of Tc99m-MDP (Technetium Hydroxymethylenediphosphonate) which had been injected prior to the bone scan. This indicates that a pair of lesions on the femur and tibia are produced due to a single event of forceful impact across the knee joint [187]. These paired bone bruises on MRI or increased uptake on SPECT are thought to be caused by impact injury of the femur on the tibial plateau.

The location of bone bruises allows speculation regarding the injury mechanism, including areas of impact and joint position. Similar lesions have been found on the posterolateral aspect of the tibia and the anterolateral aspect of the femur in approximately 80% of patients with an acute ACL injury [176,188-190]. These are most likely caused by a valgus force when the tibia is in anterolateral subluxation after the ACL is torn [190].

Gender differences in MRI patterns of ACL tears have been noted. While females more commonly undergo imaging in the acute stage and more commonly demonstrate posterolateral tibial bone bruises, males generally have a more severe presentation than females and are associated with more severe bruises on the lateral femoral condyle and soft tissue injuries [191]. Since the posterolateral portion of the tibia and anterior portion of the lateral femoral condyle are typical locations of paired bone bruises found in ACL injury, it is hypothesized that the knee motion during the injury process may be identical across genders. More severe presentation of bone bruises in males can be explained by the greater force involved in disrupting the ACL in males compared to that in females. This greater force may also create more soft tissue damage in the knee joint in males than in females. However, there are no data available to clarify the reason for this gender difference and further investigation including a larger sample size would be necessary to assess differences in the injury mechanism between males and females.

Since a bone bruise is assumed to be caused by a strong impact or sudden compressive force, an analysis of the distribution of bone bruises may indicate the sequence of joint positions during injury. Kaplan et al. [192] reviewed 215 consecutive MRI studies of acute knee injury or trauma in order to identify any possible association between the bone bruise at the posterior lip of the medial plateau and ACL injury. Twenty-five (12%) of all MRI showed a contusion at the posterior lip of the medial tibial plateau, all of which had ACL tear, while 24 images showed bone bruises in the lateral compartment in the femur and tibia. They proposed the following sequence of events in ACL injury: 1) the ACL is torn; 2) lateral bone bruises in the femur and tibia are caused by anterior translation of the lateral tibial plateau; 3) medial bone contusion in the femur and tibia are caused by anterior translation of the medial tibial plateau as a contrecoup mechanism; and 4) the joint position is reduced to the normal position. When this assumption is applied to knee motion during sports, the knee would have been in internal rotation and valgus at 2) and in external rotation and varus at 3). However, video analyses showed an externally rotated tibia at foot strike followed by valgus collapse at the end of the sequence [49], which disagrees with the hypothesis by Kaplan et al. [192]. Even though Kaplan's assumptions are not validated by video analyses, this study should not be overlooked because further analyses of bone bruise locations may contribute to understanding the sequence of joint positions at the time of injury.

Viskontas et al. [193] reported that subjects with noncontact ACL injury demonstrated a significantly higher prevalence of medial tibial plateau bone bruises than subjects who sustained contact ACL injuries. They attributed this finding to sagittal plane loading instead of valgus loading, thus resulting in concomitant collisions between the medial and lateral compartments of the tibia and femur as the tibia undergoes anterior subluxation relative to the femur. However, this paper did not conclude that medial compartment bone bruise patterns are associated with a particular loading mechanism during ACL injury.

Two-dimensional analysis on MRI images provides insufficient information to discuss the joint positions, and true 3-dimensional analysis to determine the possible knee positions would be required. Moreover, small areas of damage in the joint should also be taken into account because all damage in the intra-articular tissues would have a

mechanical cause in traumatic injury. Therefore, further study is needed to demonstrate the sequence of the knee motion during injury by carefully analysing bone bruises and other lesions in the knee.

Basic science of ACL loading

In vitro studies: Understanding the effects of internal forces, especially ligament and muscle loads as well as external forces on ACL strain will be important to clarify the non-contact ACL injury mechanism. Investigations of ACL strain behaviour with the knee flexed to less than 300 provide the most useful information. The ACL was shown to be most lax at 350, and external rotation of the tibia relaxed the ACL throughout the full range of motion as shown by Kennedy et al. in 1977 [194]. Bach [125] developed a 6-degrees-of-freedom knee simulator to measure strain on the anteromedial and posterolateral bundles (AMB and PLB, respectively) of the ACL under anterior shear load, during which the ACL strain was constantly increased in both bundles from 120o to 0o of knee flexion. Therefore, the ACL is in higher tension during extension due to constant anterior shear force on the tibia.

Effects of muscle loads change the strain on the ACL. ACL strain measurements during open kinetic chain knee extension with an isolated quadriceps force in vitro showed a significant increase in the ACL strain between 00 and 450 of knee flexion [195,196]. Using a Hall effect strain gauge, ACL strain during active knee extension between 0o and 200 did not decrease when hamstring contraction was added to quadriceps contraction [124]. The in situ force measurement using a robot/universal force sensor system also demonstrated that hamstring contraction did not reduce the ACL force between 0o and 300 [129]. Bach [125] measured the strain on the AMB and PLB during knee extension under anterior shear force and quadriceps and hamstring loading. While the strain on the AMB was reduced by half with application of a hamstring load near full extension, strain on the PLB was not reduced at full extension. Therefore, hamstring load may reduce only the AMB force near full extension under the presence of a quadriceps force. Other muscles around the knee joint, such as the gastrocnemius, popliteus, sartorius and gracilis, have not been studied in vitro and their effects on ACL strain are currently unknown.

Since "twisting" is a common subjective report at the time of the injury, the ACL strain with rotational moments should be discussed. An ACL strain measurement in vitro indicated that the ACL was slightly lax under a valgus load but tightened slightly under a varus load at 300 of flexion [194]. Neither pure internal/external rotation nor pure varus/valgus knee torque significantly strained the AMB measured at 0o, 15o and 300 knee flexion using a 5-degrees-of-freedom knee simulator [197]. A similar study showed, however, that a small, but significant percentage of the varus-valgus load was carried by the ACL throughout the full range of motion and that there were only small variations with flexion angle [198]. Although pure rotations may not increase the ACL force significantly, valgus torque in combination with anterior shear force, as well as internal tibial rotation in combination with anterior force resulted in a significantly larger strain than pure anterior force [125,199]. Moreover, Markolf et al. [199] and Bach [125] agreed that internal tibial torque consistently generated greater forces on the ACL than external tibial torque between 0o and 900. Therefore, despite some disagreement due to experimental settings, the effect of pure valgus/varus torque on the strain of the ACL would generally be insignificant, while both pure internal rotation as well as valgus torque with anterior shear force would significantly increase the ACL strain. However, it remains unknown what contribution quadriceps force made during the valgus collapse observed on video analysis of ACL injury [49,52,163]. The quadriceps may be inhibited at valgus collapse, if the ACL is already torn and the tibia is anteriorly displaced during this event. Further study is needed to establish a reliable mechanical model.

During the past few years, tibiofemoral compression force as a part of ACL injury mechanism has been a subject of very considerable interest. Compression is the most common translation that occurs during cutting and landing activities, and could be a direct result of impact (ground reaction) forces, an indirect result from muscular stabilization or, most likely, a combination of both effects. As evidenced by the common association of bone bruises with ACL injuries, compression is a likely component of the ACL injury event. Meyer et al. [200] conducted cadaveric study to induce ACL rupture by isolated FT compression. During joint compression with 30° flexed knee position, the femur was displaced posteriorly relative to the tibia until ACL failure and then continued thereafter. It was especially interesting that the direction of tibia rotation changed from internal rotation in pre-failure tests to external rotation after failure of the ACL. These coupled motions were consistent with the findings on video analysis of ACL injuries reported by Koga et al. [169,170], and were likely due to the concave geometry of the medial facet versus the slightly convex lateral facet. Before ACL failure, there was greater displacement in the lateral compartment, producing internal tibia rotation in pre-failure tests. After ACL rupture, additional motion in the medial compartment produced external tibial rotation. This study emphasized the importance of axial compressive loading of the knee during landing in ACL injury. Furthermore, video-based studies consistently document external rotation of the tibia combined with valgus knee bending as the mechanism of ACL injury, although these motions have been suggested to occur after ACL injury.

The ACL and MCL may protect each other during valgus loading, as reported by Ma et al. [201], who utilized the robot/universal force sensor system to determine the in situ forces of the ACL and MCL in response to valgus load. The authors found that ACL deficiency can increase the in situ force on the MCL, while ACL reconstruction can reduce the in situ forces on the MCL in response to an anterior tibial load. Accordingly, the ACL appears to be protected by the MCL under the pure valgus load, which in turn confirms that the ACL is the secondary restraint against valgus knee loading. Mazzocca et al. [202] found valgus torque alone creates ACL strain only after significant injury to the medial collateral ligament. Interestingly, complete injury of the medial collateral ligament was necessary before significant injury to the ACL due to valgus torques applied in isolation. Therefore, valgus collapse is hypothesized to occur after the ACL is torn since the MCL is typically intact in the non-contact ACL injury and internal rotation of the knee at landing or deceleration may be considered a high risk motion sequence in combination with vigorous quadriceps activity to prepare for the impact. This internal rotation moment may come with movement from lateral heel contact to flat foot, during which the ground reaction force on the lateral heel tends to produce pronation, resulting in correlated internal rotation motion of the tibia.

Recent in vitro studies have simulated more dynamic and realistic ACL injury situations such as landing. Withrow et al. [203] compared the magnitude of in vitro AMB strain under sagittally symmetric impulsive axial loading with and without a valgus knee moment, simulating a jump landing with pre-activated knee muscle forces. The peak normalized strain was 30% larger for the impulsive compression loading in valgus and flexion compared with impulsive compression

loading in isolated flexion, suggesting the risk of a valgus landing position. Using a modified version of the Withrow et al. [203] testing apparatus, Oh et al. [174] simulated single-legged landing and tested the effect of axial tibial torque combined with a knee varus or valgus moment on peak AM-ACL relative strain. As a result, peak AM-ACL strain was most sensitive to the direction of axial tibial torque, especially internal tibial rotation torque, but less sensitive to the direction of the frontal plane moment. The knee model simulation clearly showed similar behaviour in that the knee valgus moment increases the ACL strain by generating a coupled internal tibial rotation before medial joint space opening can occur. Hashemi et al. [204] investigated whether application of an unopposed quadriceps force coupled with an impulsive ground reaction force could induce Anterior Cruciate Ligament (ACL) injury by performing simulations of highly dynamic/ impulsive activities in vitro. They indicated that elevated Quadriceps Pre-activation Forces (QPF) increases pre-activation strain but reduces the landing strain and is therefore protective post-landing. There is a complete lack of correlation between "total" ACL strain and QPF suggesting that the total strain in the ACL is independent of QPF under simulated conditions. This interesting result is probably due to the slope and geometry of the tibial plateau. As a result of the posterior slope of the tibial plateau, an almost fully extended knee will undergo a joint compressive force that will include an anteriorly directed shear component acting on the tibia. The force transmitted through the patellar tendon will also have an anterior shear component. In this situation, a knee extension moment will be generated by the quadriceps about the FT articulation point, forcing the tibia to move anteriorly, increasing strain in the ACL and potentially causing ACL injury. However, as soon as the contact phase of the landing is initiated, knee flexion increases rapidly and the quadriceps force also increases to reduce this flexion moment. This eventually generates an extension moment. The point that is often ignored, however, is that increased knee flexion due to ground contact will cause the tibia to angulate posterior to the femur and place the tibial plateau at an anteriorly tilted angle relative to the femur, which will change the direction of the joint reaction force so that it has a posteriorly directed shear component. A very Interesting finding was reported by Lipps et al. [205], who proposed a fatigue failure injury mechanism. Using 10 matched pairs of cadaveric knees, a knee from each pair was tested with a load of 4 times body weight (4*BW) and the other received a 3*BW load. In combination with the respective loads, both also received impulsive compression force, knee flexion moment, and internal tibial torque combined with realistic trans-knee muscle forces. The loading cycle was repeated until the ACL ruptured, a 3-mm increase in cumulative anterior tibial translation occurred, or a minimum of 50 trials was reached. Eight of the 10 knees tested under the 4*BW impact load failed, and the number of cycles to ACL failure was 21 ± 18 cycles. Similarly, under the 3*BW impact load, 5 of 10 knees failed and did so in 52 ± 10 cycles. These results suggest that the human ACL is susceptible to low-cycle fatigue failure. Cox regression analysis showed that the number of cycles to ACL failure was influenced by the simulated landing force and ACL cross-sectional area. Demonstration of a fatigue failure injury mechanism represents a paradigm shift in ACL injury mechanism research because it could explain why athletes who repeatedly perform the same manoeuvre without incident suddenly rupture an ACL. The fact that athletes perform the same cutting or pivoting manoeuvre hundreds, if not thousands of times a season means that the loading history of the ACL is potentially relevant in determining whether an injury occurs.

In vitro studies to date have suggested that the major ACL injury mechanism is knee valgus combined with anterior tibial translation and internal tibial rotations, which are induced by excessive FT compression force during sports activities. It is likely that the human ACL is susceptible to fatigue failure, and therefore, correcting improper landing knee position would make sense from an injury prevention viewpoint. However, it is uncertain whether there are gender differences involved in this phenomenon.

In vivo studies: Beynnon and co-workers established a technique for in vivo ACL strain measurement using a Differential Variable Reluctance Transducer (DVRT), which is inserted surgically into the subject's knee [143-149]. With this device, it was shown that both the isometric quadriceps contraction at 15° and squatting exercise using a sport cord caused over a 4% ACL strain, while other common rehabilitation exercises, including bicycling and isometric contraction of the quadriceps and/or hamstrings, showed smaller levels of strain [147,206]. There were no data provided regarding the effects of extreme rotational loads such as valgus and internal rotation.

However, the ability to perform sport specific movements while using invasive measurement techniques is at present limited. Previous in vivo studies therefore generally focused on, for example, muscle-tendon biomechanics and rehabilitation, rather than injury mechanism research. As an alternative, recent studies often use a biplanar image-matching technique utilizing a 3-dimensional bone model and fluoroscopic images, and ACL elongation was calculated by measuring the distance of the attachments of the ACL in the bone models. Li and co-workers [207-209] established this technique, and they found both bundles of the ACL were elongated as the knee extended from 900 of flexion to 00 during quasi-static lunge activity [207]. Myers et al. [210] compared FT rotations and translations of soft and stiff landings from a height of 40 cm in healthy males and females. Average and maximum relative anterior tibial translation, internal/external rotation, and varus/valgus were all similar between soft and stiff landings, respectively, even though the peak vertical ground-reaction force was significantly larger for stiff landings than for soft landings. The musculature and soft tissues of healthy knees seem to be able to maintain translations and rotations within a small, safe range during controlled landing tasks with differing demands. Taylor et al. [211] measured ACL strain during jump landing by marker-based motion analysis techniques integrated with fluoroscopic and Magnetic Resonance (MR) imaging techniques. Interestingly, during jump landing, average ACL strain peaked 55 ± 14 ms prior to ground impact, when knee flexion angles were lowest. The observed trends were consistent with those of an in vitro study by Hashemi et al. [204]. Torry et al. [212] investigated three-dimensional rotations and translations of healthy knees during stiff drop landings. As a result, a significant relationship between anterior tibial translation and peak knee valgus angle, lending support to the theory that knee valgus position is directly related to anterior tibial translation during this motion. This finding demonstrates that these motions are not mutually exclusive but are coupled actions and that a combined high knee valgus angle with excessive anterior tibial translation is a likely scenario for ACL injury. Utturkar et al. [213] compared in vivo ACL elongation during three static knee positions: full extension, 30° of flexion, and a position intended to mimic a valgus collapse position described in the literature, consisting of 30° of knee flexion, internal rotation of the hip, and 10° of external tibial rotation. ACL length decreased significantly from full extension (30.2 ± 2.6 mm) to 30° of flexion (27.1 ± 2.2 mm). ACL length further decreased in the valgus collapse position (25.6 ± 2.4 mm). This report supports the findings of

the aforementioned in vitro studies, which showed that external tibial rotation does not increase ACL tension force.

Computational simulation

Computational simulation can establish the relation between the measured biomechanics and ACL force. McLean et al. [214-216] developed a subject-specific mathematical model of cutting motion, such as occurs in weight-bearing sports. They found that sagittal plane loading (e.g. requiring quadriceps force with a neutral knee position) alone failed to exceed 2000N of load on the ACL, whereas a combined valgus load and quadriceps force resulted in exceeding the tensile strength of the ACL. Park et al. [217] provided unique perspectives on the effects of multi-planar loading. Finite element analysis showed that impingement between the ligament and the lateral wall of intercondylar notch could occur when the knee at 45° was externally rotated at 29.1° and abducted at 10°. Strong contact pressure and tensile stress occurred at the impinging and nonimpinging sides of the ligament, respectively. However, whether this pressure is high enough to rupture the ACL remains unknown.

A 3D specimen-specific dynamic simulation model of the knee developed by Shin et al. [218] is also a useful tool to predict the effect of various loading configurations on ACL strain during dynamic single-legged landing. This model was used to test the influence of deceleration forces on ACL strain during single-leg landing and indicated that large GRF was directed posteriorly with respect to the proximal tibia and helped protect the ACL during landing, while posterior deceleration forces helped reduce ACL strain during a run-to-stop simulation [218]. They also tested the influence of isolated valgus moment on ACL strain during single-leg landing. It has been suggested that valgus moment at the knee joint does increase ACL strain, but the physiological level of isolated valgus moment observed only in vivo may not be sufficient to rupture the ACL without concomitant damage to the MCL, because coupled tibial external rotation and increasing strain in the MCL prevent proportional increases in ACL strain at higher levels of valgus moment [219]. On the other hand, when valgus moment and tibial internal rotation moment are applied in combination, the two rotational moments can cause levels of ACL strain that may be high enough to cause ACL injury [220]. Furthermore, during landing when the combined maximum valgus moment and tibial internal rotation moments were applied, the peak contact force occurred at the posterior–lateral side of the tibial cartilage in the model that agreed with the bone bruise locations that have often been observed in acute ACL–injured patients examined by MRI.

Quatman et al. [221] recently developed a new research paradigm that incorporates a multifaceted, multidisciplinary, integration of in vivo, in vitro and in silico analyses that they term "in sim". They used this technique of multiple cross-validations to analyse FT cartilage pressure distributions during normal and injurious landing scenarios. In vivo landing data from young female athletes who subsequently sustained ACL injury were incorporated into a computer model to analyse landing mechanics. Injury simulations also were conducted based on in vivo video data of female athletes during an ACL injury event. The resultant articular cartilage load distributions compared with bone bruise patterns associated with ACL injury support a valgus collapse injury mechanism that results from tibial abduction combined with anterior tibial translation or external or internal tibial rotations.

Computational modelling is a useful tool to estimate the failure load on the ACL, which may be impossible to predict with in vivo or in vitro experimental studies. However, it requires confirmation of many variables in order to optimize the calculation and it is difficult to validate the results.

Discussion

In this review, some gender differences in the risk factors of ACL injury have been identified and females have a smaller notch size [98], an increased valgus motion at landing [38], presence of a dominant leg at landing [160], and weaker hamstring torques in dynamometric testing [155,160]. Hormonal factors and lower limb alignment have not been proven to be major risk factors. Therefore, correction of the neuromuscular factors seems to be a reasonable conclusion upon which preventative strategies can be established.
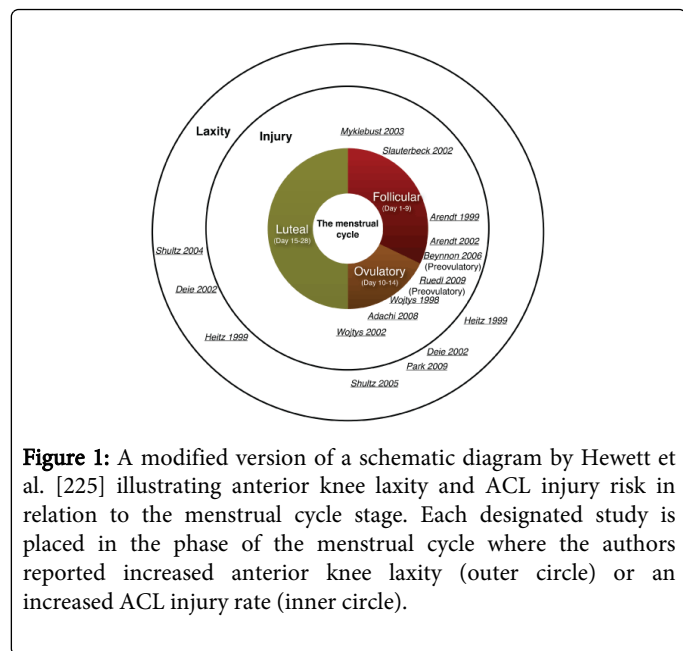
To demonstrate the mechanism of ACL injury, it is essential to determine the exact knee positions and forces applied to the knee joint at the time of injury. Although video analyses clearly show several situations at the moment of ACL injury, sufficient information has not yet been collected to build an experimental or computational model that can precisely simulate the injury. Although there is some gender difference in the size of bone bruises associated with ACL injury, none of the video analyses, questionnaire surveys or bone bruise analyses demonstrated a gender difference in the mechanism of ACL injury. A common mechanism appears to occur shortly after foot plant with the knee slightly flexed and the tibia in external rotation during decelerating activities including landing. The final consequence of the injury mechanism is a sudden valgus collapse without controlled squatting for cushioning or shock absorption. As a conclusion of this review, the mechanism of ACL injury seems to be identical across the genders. Therefore, research efforts focusing on ACL injury in females would be justified not only to identify gender differences in risk factors but also to further clarify the mechanism of injury itself.

Though a valgus collapse is a common phenomenon of the sequence in most of the injury films, it is suspected that the ACL is torn before the valgus collapse is actually seen. This is supported by the fact that the typical location of the tibial bone bruise in the lateral compartment is located too posteriorly which would not match with the femoral bone bruise without the presence of anterior subluxation of the tibia. Consequently, the next question would be "what is happening before the valgus collapse?" Some of the films appear to show that the injured knee goes slightly and instantly into varus and/or internal rotation prior to the valgus collapse, instead of into flexion or squatting down for cushioning. Since data on the strain behaviour show that internal rotation creates higher ACL strain than other positions, even a small motion toward varus and/or internal rotation under the landing force may cause a rupture of the ACL. Hence, it is expected that high-speed cameras will provide better views to clarify whether varus and/or internal rotation action is a common sequence prior to the valgus collapse. If a quick varus motion were commonly present, it would also explain why a pair of bone bruises is present in the medial compartment.

Damage distribution analysis for a patient whose injury has been filmed is also recommended to help clarify the sequence of knee motion at the time of the injury by analysing the locations of damaged tissues in the knee. Bone bruise distribution may indicate specific knee positions that create a failure load on the ACL. Even if bone bruises would only explain the knee positions after the ACL is torn, combined analyses of the injury film and bone bruises would be beneficial to explain knee motion. A more detailed analysis of tissue damage in the

knee joint after injury would also provide information to estimate the knee position or a sequence of knee positions before and/or after injury. It is also expected that more than one pattern of damage will be detected on MRI analysis, which would suggest several sequences of joint motion associated with ACL injury.

Detailed kinematic analysis during landing would be valuable in establishing detailed biomechanical models. During squatting, the femoral joint surface should glide anteriorly on the tibial joint surface due to the dominance in gliding over rolling, and the lateral femoral condyle moves posteriorly over the tibial plateau (rollback phenomenon) [222-224]. It is expected that similar kinematics will be obtained during landing, although no data are available to date. A lack of cushioning action on landing at the onset of ACL injury suggests that the kinematics would be significantly different from that of normal landing action with sufficient cushioning. Sudden termination of the cushioning action during landing may be due to mechanical restriction of the anterior glide of the femoral articular surface. Such restriction may create a book-opening joint motion (predominant rolling with a lack of gliding) to load the ACL, while causing impaction at the posterior lip of the tibial plateau due to a strong flexion moment generated by the ground reaction force. This would explain why an isolated ACL injury could occur without damaging other ligamentous structures such as the MCL. One of the possible reasons for this is instantaneous locking could be a meniscal tear or other intra-articular damage, but this hypothesis would not account for all ACL tears because not all ACL injuries demonstrate significant intra-articular damage. Another possibility is that a quick varus motion prior to valgus collapse may play a role in restricting the normal cushioning action and creating the suggested pathomechanics. There is currently a lack of information about damage distribution analyses for a series of acute ACL injuries or detailed knee kinematics during landing, which may provide some information for building a firmer hypothesis for the pathomechanics of ACL injury.

Figure 1: A modified version of a schematic diagram by Hewett et al. [225] illustrating anterior knee laxity and ACL injury risk in relation to the menstrual cycle stage. Each designated study is placed in the phase of the menstrual cycle where the authors reported increased anterior knee laxity (outer circle) or an increased ACL injury rate (inner circle).

Some neuromuscular training programs have been proven to be effective in reducing the risk of ACL injury in female athletes by correcting the varus knee action at landing or modifying the deceleration technique using a 3-step stopping technique. A knee-

over-the-toe position is emphasized in several programs as well. Since the in vitro data show that a valgus knee position with tibial external rotation creates smaller load on the ACL than does the knee position with tibial internal rotation, it would be of great interest to compare in vivo ACL strain or elongation among several possible high-risk positions of the knee. In a future cohort study, accurate kinematic analysis utilizing a biplanar fluoroscopic image-matching technique would also provide detailed information on contact kinematics in subjects who demonstrate significant valgus action at landing.

In conclusion, this issue will continue to challenge researchers and clinicians. Despite many difficulties, the most recent advances in biomechanical techniques and imaging technologies will allow further studies as suggested above to detect subtle biomechanical elements, which may provide further clues to the mechanism of ACL injury.

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