Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement

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The incidence of anterior cruciate ligament (ACL) injury remains high in young athletes. Because female athletes have a much higher incidence of ACL injuries in sports such as basketball and team handball than male athletes, the IOC Medical Commission invited a multidisciplinary group of ACL expert clinicians and scientists to (1) review current evidence including data from the new Scandinavian ACL registries; (2) critically evaluate high-quality studies of injury mechanics; (3) consider the key elements of successful prevention programmes; (4) summarise clinical management including surgery and conservative management; and (5) identify areas for further research. Risk factors for female athletes suffering ACL injury include: (1) being in the preovulatory phase of the menstrual cycle compared with the postovulatory phase; (2) having decreased intercondylar notch width on plain radiography; and (3) developing increased knee abduction moment (a valgus intersegmental torque) during impact on landing. Well-designed injury prevention programmes reduce the risk of ACL for athletes, particularly women. These programmes attempt to alter dynamic loading of the tibiofemoral joint through neuromuscular and proprioceptive training. They emphasise proper landing and cutting techniques. This includes landing softly on the forehead and rolling back to the rearfoot, engaging knee and hip flexion and, where possible, landing on two feet. Players are trained to avoid excessive dynamic valgus of the knee and to focus on the “knee over toe position” when cutting.

The incidence of anterior cruciate ligament (ACL) injury remains high, especially in young athletes aged 14–19 years. In spite of the fact that some successful prevention programmes have been introduced, ACL injury continues to be the largest single problem in orthopaedic sports medicine, with the incidence of non-contact ACL tears being much higher in female athletes in sports such as basketball and team handball than in male athletes.

As ACL injury remains a significant problem, especially in young female athletes, procedures for improved prevention and management are needed. The mechanism of ACL injury is an important focus of discussion, as an ACL tear is more often a non-contact event with a deceleration or a change of direction manoeuvre than a contact or direct blow injury. A prophylactic neuromuscular and proprioceptive training programme may reduce the number of ACL injuries in female athletes.

The President of the International Olympic Committee (IOC) Jacques Rogge stated in 2001 that “the most important goal of the IOC Medical Commission is to protect the health of the athlete”. The IOC Medical Commission therefore invited a group of physicians, physical therapists, biomechanists and scientists active in ACL research to review current evidence relating to risk factors, prevention programmes and the need for further research concerning non-contact ACL injury in young female athletes.

EPIDEMIOLOGY OF ANTERIOR CRUCIATE LIGAMENT INJURIES

The incidence of ACL injuries in the sporting population has been estimated from a variety of sources including data on surgical reconstructions. Three national ACL surgical registries have been established (Norway 2004, Denmark 2005 and Sweden 2006)1 to gather information on the details of ACL surgery and to monitor the outcomes of this surgery. Information is gathered through a registration form completed by the surgeon postoperatively. From these registries we can estimate an incidence of ACL injury, although this number under-represents the true incidence as non-operative ACL injuries are not captured.

From the Norwegian data, a total of 2793 primary ACL ligament reconstruction operations were registered by 57 hospitals during 18 months. This corresponds to an annual population incidence of primary ACL reconstruction surgeries of 34 per 100 000 citizens (85 per 100 000 citizens in the main at-risk age group of 16–59 years). The number of ACL operations differs between the sexes in the second decade of life, with females having the most ACL reconstructions in the 15–19-year age group (fig 1).1

In looking at a possible difference between the sexes, in 2005–6 the Swedish Registry found a higher proportion of both primary ACL reconstructions and revisions in men than in women (59% vs 41% and 55% vs 45%, respectively). In an active German population the overall incidence was 70 per 100 000 citizens in the more physically active proportion of the population.2 In Sweden the incidence of ACL injury in the population aged 10–64 years was 81 per 100 000 citizens.2

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ACL injuries: select sports

Looking at the ACL injury rates produced in select sports, the National Collegiate Athletics Association (NCAA) Injury Surveillance System (ISS) provides us with a unique 16-year sample of 15 sports across a college age group (typically 18–23 years). The ISS is a collection of data from representative colleges and universities (15% on average) and is not a registry. Approximately 5000 ACL injuries were reported over 16 years, producing an average of 313 injuries per year in the sample. Assuming the sample represents 15% of the total population, this equates to an average of more than 2000 ACL injuries in these 15 activities per year. If the number of reported injuries is considered, American football produced the greatest number of ACL injuries. However, if ACL injuries are ranked as a percentage of ACL injuries on a team compared with all injuries on that team, female sports dominate the list (female football/soccer, female lacrosse, female gymnastics and female basketball; fig 2A). If the ACL injury rate per 1000 exposures is considered, female gymnastics rate first with men’s spring American football second, closely followed by female football/soccer, female basketball and men’s in-season American football (fig 2B).

Taken as a whole, the most common mechanism of ACL injuries for the sports commonly associated with this injury was non-contact in nature. The exceptions were men’s American football, men’s ice hockey and men’s wrestling.

The NCAA data report exposures as one session of sport (either practice or play) and do not record exposure in terms of hours. In this data set, the largest difference in injury rate (injury/athletic exposure x1000) between the sexes was in football/soccer (females twice that of men) and basketball (females three times that of men). Despite significant changes in the pace of the game of football/soccer and basketball and the improvement in sport-specific skills of females in general, the rate of non-contact ACL injury has remained stable over the 16-year period of NCAA data collection.

For the age group slightly younger than college level (14–18 years), the rate of non-contact ACL injuries in soccer was twice as high in females as in males. For basketball the rate of injury in the younger female age group is the highest—nearly four times that of males. The ratio of male to female injuries decreases slightly at the college level and approximates 1 at the professional level (table 1).

Alpine skiing

There are no consistent data regarding differences between the sexes in the incidence of ACL injuries in recreational skiing, but female competitive alpine skiers have an incidence rate twice that of male competitive alpine racers. Other studies have reported that recreational skiers have the highest incidence of injuries while expert skiers have the lowest incidence.

The best longitudinal data in this sport are from a 34-year case-control study in a single ski area in northern Vermont. During this time there were 6 780 940 skier visits and these were associated with 18 692 injuries, of which 2539 (14%) were ACL tears. Since 1991 there has been a 40% decrease in the rate of ACL injuries, with the incidence at the present time being one ACL injury per 3101 skier visits. Women constituted 40% of the control population but suffered 63% of all ACL injuries. The risk ratio for women sustaining ACL injuries averaged 2.5 times that of men in the time period of this study.

Team handball

Several studies have reported the incidence of ACL injuries in team handball. A retrospective study found that the incidence of ACL injury was highest in women playing at the top level (0.52 ACL injuries/1000 playing hours) compared with 0.31 injuries/1000 playing hours in men. The relatively high incidence of ACL injuries in female players—particularly elite
players—has been confirmed by later prospective studies.6 7 The highest incidence of ACL injuries occurred in female elite handball in Norway with 2.29 ACL injuries/1000 match hours. The incidence of ACL injury is high in team handball compared with other team sports such as football/soccer, basketball and volleyball. However, a direct comparison between the studies is difficult because different methods were used to collect and analyse the data and the way in which the incidence of ACL injuries was reported was inconsistent. Some report the number of injuries per 1000 playing hours while others report the number of ACL injuries/1000 athlete exposures. Nevertheless, all studies have found that women have a higher incidence of ACL injuries than men.

The incidence rate of ACL injuries in all sports studied appears to be significantly greater during competition than during training and this finding is consistent among sports.8

**RISK FACTORS FOR ACL INJURY**

The fundamental basis for knee trauma prevention research is that injuries are not random events; instead they occur in patterns that reflect underlying causes. Understanding the underlying causes—or risk factors—for one of the more severe sports-related knee injuries—an ACL disruption—is important for the development of intervention strategies and for identifying those at increased risk of injury. This provides a target group for intervention.

The risk factors for ACL injury have been considered as either internal or external to an individual. External risk factors include type of competition, footwear and surface, and environmental conditions. Internal risk factors include anatomical, hormonal and neuromuscular risk factors.

**External risk factors**

**Competition in games versus practice**

Very little is known about the effect of type of competition on the risk of an athlete suffering ACL injury. Myklebust et al8 reported that athletes are at a higher risk of suffering an ACL injury during a game than during practice. This finding introduces the hypothesis that the level of competition, the way in which an athlete competes, or some combination of the two increases an athlete’s risk of suffering an ACL injury.

**Footwear and playing surface**

Although increasing the coefficient of friction between the sports shoe and playing surface may improve traction and sports performance, it also has the potential to increase the risk of injury to the ACL. Lambson et al10 found that the risk of suffering an ACL injury is greater in football athletes who have boots with a higher number of cleats and an associated higher torsional resistance at the foot-turf interface. Olsen et al10 reported that the risk of suffering an ACL injury is greater in female team handball athletes who compete on artificial floors that have a higher torsional resistance at the foot-floor interface than in those who compete on wood floors. This relationship did not exist for male athletes.

**Protective equipment**

Functional bracing appears to protect the ACL-deficient knee of alpine skiers from repeated injury; however, the effect of these braces on an ACL graft is inconclusive and requires more study. Kocher et al11 studied professional skiers with ACL-deficient knees and found a greater risk of knee injury in those who did not wear a functional brace than in those who did use a brace (risk ratio 6.4). McDevitt et al12 performed a randomised controlled study of the use of functional braces in cadets attending the US military academies who underwent ACL reconstruction. At the 1-year follow-up the use of functional bracing did not affect the rate of ACL graft re-injury. It is important to point out that there were only three injuries among those in the unbraced group and two injuries in the braced group. This was an impressive study that required considerable work, and a larger sample size that produces more re-injuries may carry with it the capability to determine whether or not functional bracing can reduce the likelihood of ACL graft injury.

**Meteorological conditions**

For sports that are played on natural or artificial turf, the mechanical interface between the foot and playing surface is highly dependent on the meteorological conditions. However, very little is known about the effect of these variables on an athlete’s risk of suffering an ACL injury. Orchard et al8 found that non-contact ACL injuries sustained during Australian football were more common during periods of low rainfall and high evaporation. This work introduces the hypothesis that meteorological conditions have a direct effect on the mechanical interface (or traction) between the shoe and playing surface, and this in turn has a direct effect on the likelihood of an athlete suffering an ACL injury.

**Summary and future directions for external risk factors**

- The evidence regarding an athlete’s complete external and internal risk factor profile for ACL injury is unclear because most of the investigations have studied isolated variables. Only the investigation by Uhorchack et al14 used a multi-variate approach to establish a selection of risk factors that are associated with an athlete’s risk of suffering an ACL tear.
- Very little is known about the effect of sport-specific factors (eg, rules, referees, coaching), meteorological conditions (eg, traction at the shoe-surface interface), playing surfaces and protective equipment on the risk of suffering an ACL injury. These potential risk factors merit further investigation.
- Little is known about the effect of age, athleticism, skill level, psychological characteristics and prior knee injury as risk factors for ACL injury. For example, almost everything that is known about the incidence rate of ACL injuries in specific sports has come from studies performed in

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**Table 1** Rate of anterior cruciate ligament (ACL) injuries relative to age

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Rate in females</th>
<th>Rate in males</th>
<th>Ratio of females to males</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school</td>
<td>0.09</td>
<td>0.02</td>
<td>4.50</td>
</tr>
<tr>
<td>Collegiate</td>
<td>0.29</td>
<td>0.08</td>
<td>3.63</td>
</tr>
<tr>
<td>Professional</td>
<td>0.20</td>
<td>0.21</td>
<td>0.95</td>
</tr>
</tbody>
</table>

These data suggest that the rate of ACL injuries decreases as female athletes mature and the level of play increases.
precollegiate (high school) and collegiate athletes. There are very few data on the incidence of ACL disruptions in subjects that are younger or older than this narrow age group and, consequently, the effect of age on the likelihood of suffering an ACL tear is not well understood.

Internal risk factors
Anatomical risk factors
Abnormal posture and lower extremity alignment (eg, hip, knee and ankle) may predispose an individual to ACL injury by contributing to increased ACL strain values; alignment of the entire lower extremity should therefore be considered when assessing risk factors for ACL injury. Unfortunately, very few studies have studied alignment of the entire lower extremity and determined how it is related to the risk of ACL injury. Most of what is known has come from investigations of specific anatomical measures.

Notch size and ACL geometry
The dimensions of the intercondylar notch have been the most discussed anatomical feature in the published literature in relation to acute ACL injuries. Geometric differences in the size and shape of the ACL have not been well characterised. In general, studies on ACL geometry and notch dimensions are difficult to interpret because of the lack of standardised methods to obtain the data. Despite the number of methods for measuring the notch, notch width measurement of bilateral knees with ACL injury is smaller than that of unilateral knees with ACL injury, and notch widths of bilateral and unilateral knees with injury to the ACL is smaller than notch widths of normal controls. This implies a strong association between notch width and ACL injury.13

In trying to understand the relationship between a small notch and the risk of ACL injury, the size of the ACL has been reviewed. Methods to determine both notch size and ACL dimensions include radiographic, MRI and photographic techniques. Despite these differences, recent reports have concluded that the ACL is geometrically smaller in women than in men when normalised by body mass index. The properties of the ACL material may differ between the sexes, and there might be an additional link to the association between notch width/ACL size and ACL injury.

Posterior tibial slope
A highly significant correlation has been reported between the posterior inferior tibial slope and anterior tibial translation.19 It is well known in the veterinary literature that tibial plateau levelling osteotomies are of value for the treatment of cranial arthritis remain areas for future research.

Summary and future directions for anatomical risk factors
- Although there is good evidence to suggest an association between a smaller width of the intracondylar notch and an increased risk of ACL injury and, on average, females have smaller notches than males, the causal relationship between the two are probably related to a smaller notch housing a smaller ACL.
- The internal-external rotatory laxity of the tibia relative to the femur is difficult to measure. There is a spectrum of biological variation and the threshold between normal and pathological behaviour is not known. Its role in ACL injury and its consequences remain unknown.
- Anatomical risk factors may not be easy to correct; however, it is important to understand them if we are to be able to identify those at increased risk of an ACL injury.

Hormonal risk factors
Structure and mechanical properties of the ACL
Studies characterising the structure and mechanical properties of the ACL indicate that women have smaller ACLs that may have lower tensile linear stiffness, are characterised by less elongation at failure and lower energy absorption and load at failure than men.19–20 These differences are not explained entirely by dimensional characteristics (ie, difference in size between men and women). This is supported by similar sex differences in the structure and mechanical properties (greater elongation, greater strain and lower stiffness in women) of the medial gastrocnemius and patellar tendons, which are also not explained entirely by anatomical differences and tendon size.

At the more macroscopic level, women also have greater tibiofemoral joint laxity (ie, anterior knee laxity, genu recurvatum) and lower joint resistance to translation and rotation.25–27 These differences are not limited to the sagittal plane but are also reflected in frontal and transverse plane motion.25–26 Together, these findings indicate that a broad physiological mechanism (eg, hormone control, differences in articular geometry, collagen turnover) may explain these sex differences, which have been implicated in ACL injury.

Although the causes/mechanisms of these sex differences are not well understood, the identification of sex hormone receptors (eg, oestrogen, testosterone, relaxin) on the human ACL19–31 has prompted studies of the potential of sex hormones to affect the structure, metabolism and mechanical properties of the ACL. To date, no specific mechanism has been identified by which hormones influence the biology and physiology of the ACL, but there is enough evidence to suggest that hormones are significant factors in the normal biology and physiology of collagen, muscle and bone.

The conflicting findings to date are in large part due to our poor understanding of this complex system, and unfortunately the various models used to examine these relationships are often not directly comparable. To understand the full effects of hormones on soft tissue and ACL injury, researchers must:
- Consider the effects of oestrogen, progesterone and testosterone (at a minimum) on knee injuries in regularly menstruating, physically active women. The relevance of various animal studies (because of their physiological differences, oestrus cycles) are of unknown significance to the human ACL and other soft tissues.19
- Account for the individual variability in hormone profiles and thus their effects (eg, injury, laxity and other soft tissue differences). This individual variability is significant and methods (especially sampling techniques) used to examine
such parameters of menstrual cycle phase and hormone levels must reflect this complexity. Although the questionnaire-based method of characterising “phasing” of the menstrual cycle is convenient, it does not provide an accurate representation of a female’s hormone milieu.\textsuperscript{36} Further, studies that examine joint laxity, muscle properties and biomechanics at a single time point per cycle phase are not adequate to identify the parameters of interest, and this approach does not reflect the complexity of the variations in the magnitude, timing and relative phasing of hormone changes across the female menstrual cycle, even among women who have a “normal” 28-day cycle.\textsuperscript{36} In addition, the effects of hormones are not immediate but occur with a time delay. It is therefore important to capture the hormone profile on days leading up to injury or testing.

- Understand how normal training, competition and stress (injury, environment, etc) alter the female hormone milieu and their ultimate effects on musculoskeletal tissue.

- Realise that the effects of hormones and their ultimate effects on soft tissue structures are on a continuum. Oestrogen, progesterone and testosterone are present in both men and women, with concentrations of individual hormones varying widely both within and between sexes. Similarly, men and women vary widely in joint behaviour (joint laxity and stiffness) and neuromuscular control. Although women are, on average, more prone to these extremes, men also experience large variations.

It is clear that there are sex differences in muscle performance. It is well accepted that mechanical loading will affect the biology and physiology of tendons and ligaments. However, the extent to which absolute hormone concentrations or variations across the cycle augment or inhibit tissue remodelling in response to mechanical stress is yet to be understood.

**ACL injury and the menstrual cycle**

There appears to be a consensus emerging from the literature that the likelihood of incurring an ACL injury does not remain constant during the menstrual cycle, with a significantly greater risk during the preovulatory phase than during the postovulatory phase. Initial work by Wojtys et al\textsuperscript{37} used self-reported menstrual history data to characterise the menstrual status of a subject at the time of injury and demonstrated a significantly greater prevalence of non-contact ACL injuries among women athletes during the preovulatory phase of the menstrual cycle. In a subsequent study by the same group,\textsuperscript{37} urine levels of oestrogen, progesterone and luteinising hormone metabolites were used to characterise a subject’s menstrual status at the time of injury. This confirmed that significantly more ACL injuries occurred during days 9–14 of a 28-day cycle with fewer injuries than expected during the postovulatory phase (defined as day 15 to the end of the cycle). Arendt et al\textsuperscript{38} found that female athletes were at increased risk of suffering an ACL injury during the preovulatory phase of their menstrual cycle compared with the postovulatory phase. Slaterbeck et al\textsuperscript{39} also reported a disproportionally greater number of ACL injuries during the preovulatory phase of the menstrual cycle, with fewer injuries occurring as the cycle progressed. In a study of recreational alpine skiers, serum concentrations of progesterone and oestradiol were used to stage the phase of a skier’s menstrual cycle at the time of ACL injury.\textsuperscript{40} Skiers in the preovulatory phase of their menstrual cycle were significantly more likely to suffer an ACL tear than those in the postovulatory phase (odds ratio 3.22). A comparison between this investigation and the previous study by Wojtys et al revealed a striking similarity. In the study of recreational alpine skiers, 74% of the women with ACL injuries were in the preovulatory phase of their menstrual cycle and 26% were in the postovulatory phase. Likewise, Wojtys et al\textsuperscript{37} found that 72.5% of the women not using oral contraception experienced ACL injuries during the preovulatory phase of their menstrual cycle compared with 27.5% during the postovulatory phase. In contrast, Myklebust et al\textsuperscript{41} studied competitive European team handball players over 3 years and found an increased risk of ACL injury during the week before or just after the onset of menstruation.

The stabilising effect of oral contraceptives on the female hormone profile and our understanding of their ultimate impact (both acute and chronic) on soft tissue behaviour, injury or performance is yet to be defined. It is important to realise that the type (ie, progesterone only versus combined oestrogen and progesterone compounds) and dosage varies widely among oral contraceptives, and both endogenous and exogenous levels must be accounted for. There is no conclusive evidence that oral contraceptives have a protective effect specifically against ACL injury.

**Summary of hormonal risk factors**

- Women have smaller ACLs that may have lower linear stiffness, less elongation at failure and lower energy absorption and load at failure compared with men. Women also have greater joint laxity and decreased muscular stiffness. While the specific causes/mechanisms for these sex differences are not well understood, hormonal involvement is implicated as they extend beyond pure anatomical differences.

- Research to date suggests that oestrogen alone is probably not responsible for changes in the structure, metabolism and mechanical properties of the ACL as interactions with cyclic loading and other hormones appear to alter the effects of oestradiol. However, the role of other sex hormones (eg, relaxin, progesterone, testosterone) in the biology and pathology of the ACL are poorly understood.

- Although animal studies have improved our understanding of the effects of hormones on the mechanical and metabolic properties of the ACL, their clinical relevance to the human ACL is questionable.

- Hormone profiles vary widely among women with regard to the timing, phasing and amplitude of hormone changes across the cycle. This variability suggests that some women may experience greater effects of sex hormones on ligament biology than others, potentially exposing those individuals to greater changes in structural integrity and risk of injury.

- There is a paucity of clinical research examining these effects in women who are oligomenorrheic or use contraceptive hormones, and who represent a large percentage of the physically active female population.

- There appears to be mounting evidence that women are at a significantly greater risk of ACL injury during the preovulatory phase of the menstrual cycle than during the postovulatory phase.

**Future directions**

- Future basic science studies investigating the effects of hormones on the structure, metabolism and mechanical properties of collagen should examine all relevant hormones at their normal physiological concentrations using models relevant to the physically active female.
It is critical that study designs address the complexity of the female menstrual cycle, including the potential time delay effects and individual variations in hormone profiles. Sampling at multiple time points within a phase is recommended.

Future studies should extend beyond normal menstruating females and examine the effects of hormone variations (amenorrhoea, oligomenorrhoea, oral contraceptive use) on both acute and chronic soft tissue changes and the potential for injury.

Limited evidence suggests that hormones may modify the normal remodelling effects of collagen secondary to mechanical loading. Future studies should examine these effects in combination using models relevant to the physically active female.

Future studies should aim to examine how normal training, competition and stress (injury, environment) alter the female hormone milieu and their ultimate effects on musculoskeletal tissue.

MECHANISMS FOR NON-CONTACT ACL INJURIES

To develop specific methods for preventing sports injuries, it is important to understand the causative event or mechanism of injury, as outlined by Bahr and Krosshaug. A number of different methodological approaches have been used to study the mechanisms of injury in sports. These include interviews with injured athletes, analysis of video recordings of actual injuries, clinical studies (where the clinical joint damage is studied to understand the mechanism of the injury), in vivo studies (measuring ligament strain or forces to understand ligament loading patterns), cadaver studies, mathematical modelling and simulation of injury situations, or measurements/estimation from “close to injury” situations.

Video analysis

Video analysis is essential as it is usually the only way to obtain kinematic information from the actual event. In rare cases, injuries have even occurred during biomechanical experiments, but for obvious ethical reasons we cannot base our research on this approach. Six studies have used video analysis to study non-contact ACL injury mechanisms in sports (table 2).

These studies were in general agreement that injuries occurred in cutting or landing situations. The knee was reported to be relatively straight at the point of injury. All the studies agreed that knee valgus was seen frequently. Boden et al found that the amount of internal/external rotation at the time of rupture was minimal. This agrees with the findings of Olsen et al where the amount of internal/external knee rotation was 10° or less in 90% of the cases. However, the interpretation of the findings varied considerably. Olsen et al stated that valgus loading in combination with external or internal knee rotation caused the injury and proposed notch impingement as a plausible cause of the excessive ACL loading. Boden et al and Teitz, on the other hand, hypothesised that a vigorous eccentric quadriceps contraction was the main cause.

Unfortunately, the reported variables among the studies using the visual inspection approach are non-standardised, making it difficult to compare them. Another major limitation of these studies is that all except one are based on visual inspection. Krosshaug et al validated the visual inspection method and found the accuracy and precision among six experienced ACL researchers to be poor. For example, it was found that the true knee flexion angle was generally twice as high as the estimate. When the analysts estimated 30° knee flexion, the true angle was 50–60°. Results from studies based on this method must therefore be interpreted with great caution.

To overcome the inherent difficulties of visual inspection of human motion from video, Krosshaug et al developed a novel and versatile technique using model-based image matching from one or more camera views. In this method, 3D models of the surroundings as well as a customised skeleton model are manually matched to the background video footage. This method proved to be much more accurate with a difference in root mean square from traditional marker-based motion analysis of <12° for hip and knee flexion/extension. In a new study, Krosshaug et al demonstrated the feasibility of this method to actual injury videos. Detailed time courses for joint kinematics and ground reaction force were obtained for a four-camera basketball video and a three-camera European team handball video. The valgus angle increased abruptly in both cases, from 4° to 15° within 30 ms and from 3° to 16° within 40 ms for the basketball and handball injury, respectively. However, in order to make general statements on typical injury kinematics, a systematic approach to collecting and analysing more injury videos is needed.

Biomechanical studies

Recent studies have consistently shown that the predominant forces that affect strain in the ACL are anterior-directed shear forces applied to the tibia (either from external sources such as an anterior-directed force applied to the back of the lower leg or

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total</th>
<th>No. analysed</th>
<th>Methods and materials</th>
</tr>
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<tr>
<td>Boden et al</td>
<td>27</td>
<td>15</td>
<td>Visual inspection and questionnaires. Videos obtained from professional and collegiate teams: football (56%), basketball (30%), soccer (9%), volleyball (4%), 7 women, 16 men</td>
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<td>Ebstrup et al</td>
<td>15</td>
<td>3</td>
<td>Visual inspection. Prospective collection of videos from Danish indoor ball games. Two representative handball injuries and one basketball injury analysed. All women</td>
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<td>Teitz et al</td>
<td>54</td>
<td>14</td>
<td>Visual inspection. Retrospective multicentre video analysis: 20 basketball, 18 football, 9 soccer injuries. Only basketball injuries analysed. 3 men, 11 women</td>
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<tr>
<td>Olsen et al</td>
<td>20</td>
<td>19</td>
<td>Visual inspection and questionnaires. Retrospective and prospective video collection of women’s Norwegian or international handball competition</td>
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<td>Krosshaug et al</td>
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<td>30</td>
<td>Visual inspection. Retrospective video collection from high school, college and NBA, WNBA basketball. 13 men, 17 women</td>
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<tr>
<td>Krosshaug et al</td>
<td>3</td>
<td>2</td>
<td>3D model-based image matching. One male NBA basketball player (4 camera views), one female Norwegian elite team handball player (3 camera views)</td>
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</tbody>
</table>
through internal mechanisms such as contraction of the dominant quadriceps muscles with the knee near extension). Important contributions to ACL strain values come from forces applied in the coronal and transverse planes of the knee. Biomechanical data have come from cadaveric studies of knees, strain gauges placed in vivo at the time of surgery and from analytical modeling. Cadaveric studies show that anterior-directed shear forces create most strain in the ACL with some added increase from varus, valgus and internal rotation moments.51-53 External torque applied to the knee produces relatively low ACL strain values. Valgus torque alone creates ACL strain only after significant injury to the medial collateral ligament. Interestingly, complete injury to the medial collateral ligament was necessary before significant injury to the ACL due to valgus torques applied in isolation.54 These cadaveric studies emphasise the importance of anterior shear forces in ACL injury.

With the knee near full extension, contraction of the quadriceps muscle—and the resulting force developed in the patellar tendon—produces an anterior-directed shear force on the proximal aspect of the tibia that strains the ACL. The ACL strain values are proportional to the magnitude of force in the patellar tendon and the angle of flexion of the knee. The patella tendon forms an angle with the tibia and its geometric orientation is able to produce ACL strain when the knee is near extension. An impulsive load applied to the patellar tendon with the knee in slight flexion has the potential to create an injury to the ACL.55 Application of patellar tendon force alone could cause enough ACL strain to alter it grossly and to increase anterior knee laxity. Application of impulse to a cadaveric knee flexed at 25° increased strain in the ACL. When the impulse was applied 15° out of the knee flexion plane to create a valgus force, the amount of strain was increased.56

In vivo studies have produced similar conclusions. Strain gauges were placed on the ACL after arthroscopic surgery in which the ACL was normal. The gauges were left in place long enough for the subjects to recover and perform rehabilitation exercises with moderate contraction of the leg musculature.57 Strain in the ACL is affected by anterior-directed shear loads applied to the tibia (relative to the femur) and a little by varus/valgus torques. Rehabilitation exercises can also produce significant strain in the ACL. Exercises that include contraction of the quadriceps in isolation with the knee near full extension produce high ACL strain values, while co-contraction of the hamstring muscles in combination with contraction of the dominant quadriceps muscles reduces ACL strain values in comparison to contraction of the quadriceps muscle group in isolation. Strain gauges have been implanted in subjects undergoing a high speed stop jump. The ACL was strained before heel strike and reached a maximum value very close to the maximal ground reaction force at landing.58 Cadaveric and in vivo studies have not clearly elucidated the biomechanical factors seen in the motion analysis studies of ACL injury. These studies often show a prominent motion in the coronal plane that involves femoral adduction and internal rotation, knee flexion and valgus, tibial rotation, and foot and ankle valgus. Motion analysis studies show a complex connected combination of movements which appear as an apparent valgus in the coronal plane but probably have only a relatively small contribution from actual medial opening of the knee, which would injure the medial collateral ligament if all the apparent valgus was isolated to coronal plane knee motion.

**Kinematic analysis**

Kinematic analysis of athletic college students revealed several differences in motion during running, side-step cutting and cross-over cutting. Women landed with less knee flexion and maintained a straighter knee during the entire stance phase. In addition to flexion, women displayed more valgus through the entire stance phase. It should be pointed out that the flexion occurs at the knee itself, while the valgus seen in the coronal plane could not have come entirely from rotation of the tibia around a stationary femur in the coronal plane but includes hip internal and external rotation combined with knee flexion. The muscle firing was assessed by electromyography (EMG). The quadriceps EMG was higher in women, with activation levels nearly twice those of the maximum EMG levels in muscle under maximum loading conditions in a dynamometer. Hamstring activity was less in women and the EMG values were only about half the level of a maximum measured by a dynamometer. ACL injuries appear to occur with hard and awkward landings on the knee when it is positioned near extension. The female knee is in more extension and has higher quadriceps activation at initial contact with the ground. The straighter knee and the higher quadriceps activation can combine to produce more strain in the ACL.59

A kinetic and kinematic analysis was performed for men and women performing a forward jump with a stop on a force plate followed by a jump slightly behind, straight above, or slightly ahead of the initial landing location.60 Inverse dynamics allowed computation of anterior shear forces which would act to produce strain on the ACL. Women had greater anterior-directed shear forces on the tibia for all jump conditions. Maximum ACL strains were observed near the initial contact period.61 Fatigue studies using a similar kinetic analysis showed that fatigue increased anterior-directed shear forces in both men and women.62

A kinematic study of young male and female football/soccer players showed that boys and girls land from a stop jump with a similar amount of knee flexion and valgus at ages 11 and 12. However, women begin to land with straighter knees progressively up to age 16.63

A mechanism seen frequently in ACL injuries involves a hard and awkward landing with the knee near extension (eg, straight). The hard landing implies high forces that are not “dampened” by hip, knee and foot motions. The “awkward” part of the landing may involve landing outside the anticipated landing manner with higher than usual abduction or valgus moments applied about the hip and knee joints.64

**Summary and future directions for mechanisms of ACL injury**

- Whole body motions related to mechanisms of injury: almost 80% of ACL injuries are non-contact in nature. Injuries often occur when landing from a jump, cutting or decelerating. A combination of anterior tibial translation and lower extremity valgus are probably important components of the mechanism of injury in these athletes.

- Likely components to the injury mechanism include: anterior translation, dynamic valgus of the lower extremity with the joint near extension, low flexion probably due to increased quadriceps activity (and this could also include increased gastrocnemius activity), most or all of the force on a single leg or foot with the foot displaced away from the body’s centre of mass and increased trunk motion.

- Potential neuromuscular imbalances may be related to components of the injury mechanism: women have more “quadriceps dominant” neuromuscular patterns than men.

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Hamstring recruitment has been shown to be significantly higher in men than in women. The hamstring to quadriceps peak torque ratio tends to be greater in men than in women.

- Because of the likely injury mechanism, it is recommended that athletes avoid knee valgus and land with more knee flexion.

Lower extremity valgus (knee abduction) loading and anterior tibial translation are likely to be involved in the mechanism. Future research should combine several research approaches to validate the findings such as video analysis, clinical studies, laboratory motion analysis, cadaver simulation and mathematical simulation.

EVALUATION OF ACL INJURY

Little is known about differences between the sexes in the evaluation of ACL injury. We therefore suggest that future studies should include large enough sample sizes to allow detection of possible sex differences in the outcomes of interest.

Natural history

There is a little knowledge about the natural history of an ACL injury. The true incidence is probably not known. With MRI as a diagnostic tool the incidence is 8 per 10 000, which has been verified by register studies. However, it can be assumed that many patients with ACL injuries are not diagnosed at the time of the injury. A proportion of these athletes will present with knee symptoms or after re-injury. Others will never be diagnosed and are either without symptoms or have adapted to the altered knee function. The proportion of these categories is unknown. In a US community-based cohort there was a prevalence of ACL injuries of 4.8% in individuals aged 50–90 years unslected for problems.

The course of an ACL injury depends on many different factors such as trauma mechanism, associated injuries, anatomical factors and activity level after the injury. There is no evidence of a sex difference. Independent of treatment, some patients will cope with their desired activity level (“copers”), some will adapt to an activity level adjusted for the knee function (“adaptors”) and others will be unable to cope with being ACL-deficient (“non-copers”). Earlier reports show that each of these groups constitutes about one-third of the population. This is supported by a recent study of primarily non-operatively treated ACLs.

Summary and future directions for evaluation of ACL injury

- The diagnosis is made by a history of sudden knee pain during strenuous activity, an inability to continue, a “pop”, haemarthrosis.

- The activity level is difficult to determine because there are no solid data on the normal decrease in activity level without injury. In the longer perspective, the level of activity does not seem to be differ with different treatments. The course is determined by whether they are copers, adaptors or non-copers. There is no accurate way to define the categories in the acute phase.

- No good data exist on the natural history of untreated lesions combined with a compliant training programme and various levels of post-injury activity levels.

- Prospective studies are needed to study the natural history of the cohort, but these are difficult to carry out.

Associated injuries

As evaluated by MRI, an isolated ACL is an infrequent phenomenon although associated ligament injuries may not be very common. In the Norwegian National Knee Ligament Registry (NLKR), a total of 2793 primary cruciate ligament reconstruction surgeries were registered by 57 hospitals. In 27 cases (1%) a lateral collateral ligament injury was reported, while a medial collateral ligament injury was reported in 129 cases (5%). Non-operative treatment of medial collateral ligament injury is effective if combined with reconstruction of the ACL.

Knees with acute ACL injuries should be evaluated for meniscus tears as these are identified in approximately 50% of cases. Lateral meniscus tears are more frequent in the acute setting while medial meniscus tears are associated with chronic ACL deficiency. In the NLKR there were a total of 1287 (47%) associated meniscus tears, 90% of which were treated surgically. In a study of ACL injury in 151 patients (56% women), 38% had an associated medial meniscus tear. ACL injury is a major long-term risk factor for the development of osteoarthritis, and no currently available treatment has been shown to reduce this risk factor. It is not clear if it is the associated meniscus tear at baseline, the development of a secondary meniscus injury, the meniscectomy or all of these that constitute risk factors for the development of osteoarthritis of the knee.

Articular cartilage lesions were reported in 712 knees (26%) in the NLKR, 59% of which were treated surgically. When grading the cartilage lesions according to the International Cartilage Repair Society classification, 222 (51%) cases were classified as grade 1, 283 (40%) as grade 2, 151 (21%) as grade 3 and 49 (7%) as grade 4 (grading was missing in 7 cases).

MRI is useful in assessing associated injuries such as bone contusions, intra-articular fractures and associated ligament injuries. One recent study has mapped out concomitant fractures and meniscus injuries and traumatic bone marrow lesions in the acute ACL injured knee by MRI and quantitative MRI (qMRI) in 121 subjects (26% women). Most of the ACL injured knees had a cortical depression fracture which was associated with larger volumes of bone marrow lesions.

Clinical examination

Physical examination

Examinations appear to detect differences in end point better than differences in displacement. Joint motion varies within a normal population but there is little left-to-right variation in normal subjects. The ACL functions as a primary stabiliser to limit anterior tibial displacement and a secondary stabiliser to restrain tibial motion. The accuracy of diagnostic tests for ACL injury has been questioned. A positive pivot shift test result is best for ruling in an ACL rupture, whereas a negative Lachman test result is best for ruling out an ACL rupture. It is also concluded that, using sensitivity and specificity values only, the Lachman test is better overall for ruling in and ruling out ACL ruptures.

The first clinical examination after an acute knee trauma has a low diagnostic value. For isolated ACLs, physical examination continues to have high specificity. Instrumented testing devices and stress radiography are used for objective measures but their use seems to be declining. Further assessment with MRI improves the chances of a correct diagnosis of intra-articular pathology and is recommended in the early phase after rotational knee trauma. The accuracy of MRI in predicting ACL injuries is 95% or more.
Outcome scores and outcome after ACL injury

During the last decade, consensus has been reached within the field of sports medicine, orthopaedics and general medicine that the primary outcome measure in clinical trials should be patient-relevant. Thus patient-reported outcomes with different focus have been developed, usually categorised as generic, joint-specific or disease-specific. For patients with ACL injury, disease-specific, joint-specific and generic instruments are used. Books and literature reviews outlining and comparing the currently available instruments for patients with knee complaints have been published.77–80

Validity, reliability and responsiveness

The most important property of an outcome measure is the responsiveness. For a measure to show high responsiveness in clinical studies, good validity and reliability are necessary prerequisites. A safe choice is therefore to choose an outcome measure with proven large effect sizes.

Validity is not an absolute or dichotomous property, and validation is a continuously ongoing process. The correlation between knee pathology and the patient’s perception is generally weak,51 indicating that, for patient-relevant outcome measures, the more important aspect is that the measure is validated for patients of similar age, sex and physical activity level rather than the specific knee pathology. A further fact in support of this view is that knee pathologies such as ACL tear, meniscal tear or cartilage injury often coincide and symptoms from specific pathologies cannot be separated.52

Score aggregation and score categorisation

Structural outcomes such as joint laxity and radiographic changes do not correlate well with patient-relevant aspects such as pain and function. Aggregating these outcomes into one total score will jeopardise interpretation of the results, and outcomes on different levels need to be reported separately.

Tapper and Hoover50 introduced a system for evaluation of symptoms and function following meniscectomy in 1969 in which they categorised outcome into four categories: excellent, good, fair and poor. This approach is appealing and the raw scores of established knee scoring scales are frequently categorised into these same four categories using arbitrarily chosen cut-off values. However, categorisation can introduce bias and lack of precision. The Lysholm scoring scale84 is a commonly used knee injury scoring scale which aggregates function and symptoms into one single score from 0 to 100 (worst to best). A cut-off of 84 points is used to categorise a good/excellent outcome. But what does a Lysholm score of 84 really represent? A patient could have a slight limp, some problems with stairs and some pain and be categorised as good/excellent with a total score of 89 out of 100. Alternatively, a patient could experience frequent instability that precludes sports activity, have some pain and yet score 85 and be categorised as having a good/excellent outcome. Most probably the patients themselves would not categorise either of these scenarios as a good/excellent outcome. Categorising the raw scores of rating scales tends to inflate the result, and the interpretation of categorical data depends on the content of the particular rating scale and the relative weight given to each component aggregated into the total score.89 Individuals rated as excellent or good on one scale may therefore be rated as only fair on another scale. Avoidance of data generalisation remains the optimal method for studying the outcome of knee injury.84

Administration mode of questionnaires

Substantial bias may be introduced if the operating surgeon answers the questionnaire.85 This also holds true for “unbiased” observers and applies to orthopaedic conditions other than ACL injury as well.86–87 Patient-relevant questionnaires should thus be self-administered (ie, filled out by the patients themselves in a neutral setting). The administration mode needs to be accounted for when comparing the patient-relevant outcomes between studies and over time within the same group of patients. The awareness of interviewer bias has increased over the years and more recently developed outcome measures are intended for self-administration.

Summary and future directions for outcome scores and outcomes

- It is important to evaluate the patient’s perspective of ACL injury.
- To minimise bias, patient-administered questionnaires should be used.
- Aggregating structural outcomes, symptoms and function into one total score will jeopardise interpretation of the results, and outcomes on different levels need to be reported separately.
- Categorising the result of a score into good/excellent, fair and poor should be avoided as this will inflate the results, introduce bias and lacks precision.

Motion analysis

ACL injury increases pathological anterior tibial translation and internal tibial rotation. Motion analysis enables detection of subtle kinetic and kinematic changes that may influence the final clinical outcome. There has been a gradual development of functional adaptations that protect the knee joint from excessive anterior translation episodes. Such a mechanism is limited quadriceps function near extension (the quadriceps avoidance pattern) and increased and prolonged hamstring activity.

Another possible mechanism of chondral damage is increased internal tibial rotation which can lead to excessive loads in cartilage areas not commonly loaded and thus contribute to future osteoarthritis. A better understanding of kinetic and kinematic changes and their final effect on the menisci and cartilage may provide useful information in the evaluation of an individual’s natural course.90–93

Summary of motion analysis

- ACL injury results in changes in kinematics, kinetics and neuromuscular activity.
- Anterior tibial translation, internal rotation of the tibia and quadriceps avoidance are typical features seen following an ACL injury. These changes most probably contribute to the development of osteoarthritis.

MANAGEMENT OF ACL INJURY

All healthcare units that service patients with knee sprains should have the capability to recognise the presence of a torn ACL or should be able rapidly to refer the patient to a clinic that can confirm the diagnosis if it is suspected.85 The treatment goals are to restore knee function, to permit the patient to return to a desired level of activity without experiencing giving way and to minimise the risk of osteoarthritis. Treatment can be either surgical with a reconstruction of the ACL followed by rehabilitation or rehabilitation alone. The literature supports both treatment regimes, but a recent Cochrane review85...
considers that good quality randomised trials are required to determine which is the preferred treatment in different situations. The decision regarding the treatment must therefore be individualised, and factors such as occupation, sports activities and associated injuries must be considered. A high activity level, specific demands and repairable meniscus injury are relative indications for subacute ACL reconstruction. If high-risk activities are not anticipated, the primary treatment option for an ACL injury is rehabilitation training for 3–4 months followed by assessment of knee function and quality of life. If re-injury occurs or the patient is not satisfied for any reason, a late reconstruction can be performed.

The major technical principles for an ACL reconstruction have become less controversial in recent years with improved knowledge of the anatomy, biomechanics and the healing process of the ACL following reconstruction. The choice of grafts has received much attention in the literature. In general there is little evidence to suggest significant differences between hamstring and bone-tendon-bone (BTB) grafts regarding short- and mid-term outcome. Reports of more degenerative changes in the tibiofemoral joint after ACL reconstruction with BTB grafts need to be verified in randomised clinical trials.

An increased failure rate in women compared with men has been reported with the hamstring graft. In another study with questionnaire power, greater anterior knee laxity over time was found in women compared with men after reconstruction with the hamstring graft. These data may support the use of a BTB graft as the first choice in women but, importantly, it must be pointed out that there is no clear correlation between laxity and functional outcome.

The double bundle technique for ACL reconstruction may have advantages regarding the long-term results since it seems to have the potential for diminishing rotational laxity. This may reduce the risk of later osteoarthritis but no data are available to support this theory. There is currently no convincing evidence that this technique results in better functional results than the single bundle procedures.

It appears that the incidence of ACL injuries among prepubescent children is similar in boys and girls. At puberty the incidence in girls becomes higher than in boys and, according to the Scandinavian ACL registries, more ACL reconstructions are performed on girls at this age. The principles for treatment of ACL injuries in this age group are not gender-specific.

The high risk of secondary injuries after the initial injury must be considered and, independent of the treatment choice, these patients must be followed carefully. A specific problem is the potential risk of growth disturbances when reconstruction of the ACL is performed before puberty.

### Rehabilitation after ACL reconstruction

Motion and immediate weight bearing postoperatively has been standard since the 1970s. Pain inhibition is a common problem postoperatively (first days) and can result in inability to activate the thigh muscles, primarily the quadriceps, irrespective of the graft used, and the hamstrings when the hamstring graft is used. Electrical muscle stimulation may therefore play an important role in the early phase of rehabilitation after ACL surgery in order to stimulate activation of the muscles and is more effective in women than in men for preventing muscle hypotrophy.

Failure to regain full knee extension after ACL reconstruction is the most common complication. Range of motion exercises with particular attention to regaining complete knee extension are therefore important and should be started during the first postoperative days. Full knee extension is individualised, with some patients having normal hyperextension. Knee extension of the contralateral leg should therefore be examined and the same degree of knee extension should be obtained in the ACL reconstructed knee.

Both closed kinetic chain (CKC) exercises and open kinetic chain (OKC) exercises for the quadriceps muscle should be used in the rehabilitation programme. OKC training should, however, be introduced cautiously, starting with a range of motion between 90° and 40° with a 10° increase every week. CKC exercises are recommended from the beginning of rehabilitation. A recent study showed greater anterior knee laxity when OKC quadriceps exercises were introduced 4 weeks after hamstring ACL reconstruction than when OKC exercises were introduced after 12 weeks. It is therefore recommended that OKC quadriceps training should not begin within 8 weeks of surgery. The same difference was, however, not found in patients with patellar tendon ACL reconstructions.

Strengthening of the hamstrings may be difficult when one or more of the muscle tendons has been removed for the graft. Quads strengthening is as important in patients with hamstring grafts as it is in patients with patellar tendon grafts. More problems were experienced with gaining strength of the hamstring muscles after ACL reconstruction with hamstring grafts than gaining strength of the quadriceps muscle after patellar tendon ACL reconstruction.

A number of authors have emphasised the importance of neuromuscular training to restore knee joint stability and regain a normal motion pattern. When using functional performance tests for evaluation, it has been found that a battery of at least three (or four) different tests should be used. Patients should be tested during non-fatigued muscle conditions as well as fatigued conditions.

There is as yet no evidence that rehabilitation after ACL reconstruction should be different for men and women. However, in 4890 patients with ACL reconstructions, increased laxity after reconstruction with a hamstring graft occurred independent of sex (Werner, unpublished 2008). No significant difference was seen between the sexes in improvement of quadriceps and hamstring muscle torques, one-leg hop test for distance, clinical outcome as evaluated by the Knee Osteoarthritis Outcome Score (KOOS) and activity level as evaluated by the Tegner Activity Scale 6–8 months after reconstruction and rehabilitation. The findings of increased laxity after ACL reconstruction with a hamstring graft may imply that rehabilitation should be slowed down after reconstruction with this graft.

### Return to sport

Shelbourne and Gray stated that: “It has become almost universally accepted that rehabilitation of the healing ACL graft with rapid return to sports that have the potential to generate high stresses in the graft and knee does not lead any deleterious effects”. Early return to sports in recent years has been advocated because of better surgical techniques and understanding of ACL biomechanics and the healing process.

Most articles published in recent years advocate a return to unrestricted sports 6 months or later following ACL reconstruction. Evidence-based evaluation has not proved that an early (2–4 months) return to sport is safe and efficacious, but it is possible to return to sports early (2–4 months) after ACL reconstruction. From the perspective of the graft and rehabilitation, it is also possible to do so with acutely injured
ACL-deficient knees without surgery. A few articles have been published that advocate return to sports between 4–6 months. These are case series which are unable to prove that such an early return is more effective or safer than a more conservative rehabilitation. High-quality evaluations have shown that early weight bearing, early mobilisation, rehabilitation without braces and early CKC exercises are safe. Return to sports following ACL reconstruction should be based on regaining function, range of motion, strength and patient’s desire (goal-based, not time-based). However, in the long term, changes in cartilage metabolism noted following ACL reconstruction must also be considered. This is important when discussing the timing of a return to demanding activities after an ACL injury/reconstruction. Cartilage metabolic MRI and synovial fluid studies indicate that ACL-injured joints do not regain their normal glycosaminoglycan (GAG) structure until 2 years after the injury. A low GAG content in the cartilage matrix is probably a risk factor for osteoarthritis, since the altered structure of the matrix may expose the collagen network and make the matrix more susceptible to the development of osteoarthritis.

Only two of the recently published randomised controlled trials and systematic reviews concerning rehabilitation following ACL reconstruction have dealt with return to sports. In a randomised controlled trial of rehabilitation following ACL reconstruction in soccer athletes, Ekstrand et al. compared a standard 6-month protocol with an extended 9-month protocol and found no differences in outcomes 1 year after surgery. In another randomised controlled trial, Beynnon et al. compared a 19-week rehabilitation programme with one that lasted 31 weeks. Exercises were instituted over different time intervals based on the amount of strain produced within the normal ACL. No differences were found in anteroposterior laxity, International Knee Documentation Committee (IKDC) clinical assessment, KOOS, one-leg hop tests, markers of cartilage metabolism or Tegner Activity Scale 2 years after surgery. Both accelerated and non-accelerated rehabilitation produced increases in the synthesis of type II collagen and proteoglycan. Both programmes appeared to affect cartilage metabolism similarly. Changes in cartilage metabolism following ACL reconstruction persist for up to 2 years. This warrants the attention of all clinicians as it may have profound effects on the eventual development of osteoarthritis, no matter what rehabilitation is undertaken.

Long-term studies have shown that about 50% of patients have radiographic osteoarthritis of the knee joint 15 years after an ACL injury, independent of treatment. However, some studies have shown a much lower prevalence. The study by Neuman et al. found no osteoarthritis after non-operative treatment if there was no secondary meniscus injury. All these studies had slow and controlled rehabilitation after the injury or after surgery, which may indicate the relevance of the GAG loss as described by Tiderius et al. It therefore seems possible to reduce the risk of osteoarthritis markedly, but it is unclear whether this is compatible with return to high demanding sports activities.

Summary of management

- The principles of treatment of ACL injuries in prepubescent children are not sex-specific. A specific problem is the potential risk of growth disturbances when a reconstruction of the ACL is performed before puberty.
- The high risk of secondary injuries after the initial injury must be considered and, independent of the treatment choice, these patients must be followed carefully.
- High quality evaluations have shown that early weight bearing, early mobilisation, rehabilitation without braces and early CKC exercises are safe.
- There is no evidence in the literature that rehabilitation should be different for men and women after ACL reconstruction.
- Return to sports following ACL reconstruction should be based on regaining function, range of motion, strength and patient’s desire (goal-based, not time-based).
- Long-term studies have shown that about 50% of patients will have radiographic osteoarthritis 15 years after an ACL injury, independent of treatment. Data are available indicating that it is possible to reduce the risk of osteoarthritis markedly. There is no evidence that the method for this reduction could be surgical, except the fact that stabilisation may lower the risk of a secondary meniscus tear. It is unclear whether this is compatible with a return to high demanding sports activities.

Remaining questions

- Is it possible to reduce the risk of meniscus tears with specific rehabilitation protocols or is the only way a surgical stabilisation?
- Is the subtle increased anterior knee laxity and coupled internal rotation often noted following ACL reconstruction safe for injured/healing articular cartilage?
- What is the effect of rehabilitation and return to sport on the meniscus, whether injured or not?
- How does the prolonged alteration in cartilage metabolism observed following ACL reconstruction affect the future status of the cartilage surfaces?
- How fast can rehabilitation and return to sport be advanced without injuring the healing ACL graft?
- What are the effects of body weight and muscle forces on graft healing?

We need more studies with high levels of evidence to answer these questions.

PREVENTION OF ACL INJURY

A growing number of injury prevention programmes targeted at reducing the risk of ligamentous knee injury in general—and ACL injury in particular—have been reported in the literature. Although a number of risk factors for ACL injury have been proposed, only the biomechanical risk factors have been examined in sufficient depth to support the design and evaluation of preventive interventions.

Most prevention programmes attempt to alter the dynamic loading of the tibiofemoral joint through neuromuscular and proprioceptive training. The studies to date focusing on biomechanical modifications have resulted in the reduction of lower extremity injuries in athletes. However, the studies vary widely both in their approach to injury prevention and the validity of the study design. Most studies to date have been non-randomised and very few have been conducted as randomised controlled trials. Despite this, we now have valuable information to assist us in preventing ACL injuries in female athletes.

Successful programmes share a number of common elements. Most include one or more of the following: traditional stretching, strengthening, awareness of high-risk positions,
high-risk positions as well as effective reaction strategies. The phantom foot ACL injury mechanism, and strategies to avoid which included proper body positioning, understanding of the high-risk situations to reduce the risk of ACL injury.

Participants also underwent an awareness training session in order to avoid high-risk behaviour and manage their skiing in order to avoid high-risk injury is summarised in table 3.

### Table 3  Relation of components of prevention programmes to specific risk factors for anterior cruciate ligament (ACL) injury

<table>
<thead>
<tr>
<th>Position</th>
<th>Intervention strategy</th>
<th>How?</th>
</tr>
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<tbody>
<tr>
<td>Extended knee at initial contact</td>
<td>Knee flexion</td>
<td>Concentric HS control and soft landing</td>
</tr>
<tr>
<td>Extended hip at initial contact</td>
<td>Hip flexion</td>
<td>Hip flexion control and soft landing</td>
</tr>
<tr>
<td>Knee valgus with tibiofemoral</td>
<td>Address dynamic control; decrease</td>
<td>Lateral hip control upon landing</td>
</tr>
<tr>
<td>Balance deficits</td>
<td>dynamic valgus</td>
<td></td>
</tr>
<tr>
<td>Skill deficiency</td>
<td>Proprioception drills</td>
<td>Dynamic balance training</td>
</tr>
<tr>
<td></td>
<td>Improve agility</td>
<td>Agility drills to address deceleration techniques and core stability</td>
</tr>
</tbody>
</table>

HS, hamstring.

### Education

Ettlinger et al. used a relatively simple approach to prevention of ACL injury in downhill skiers, attempting to modify high-risk behaviour through education and increased awareness. In this prospective non-randomised trial, 4000 on-slope alpine ski instructors and patrollers in 20 ski areas completed training and reporting requirements during the 1993–4 skiing season. The training kit included a 19 min ACL Awareness Training videotape showing 10 recorded ACL injuries sustained by alpine skiers of various levels and various written materials. The videotape used guided discovery, allowing viewers to visualise carefully selected stimuli and incorporate this information into their skiing in order to avoid high-risk behaviour and manage high-risk situations to reduce the risk of ACL injury. Participants also underwent an awareness training session which included proper body positioning, understanding of the phantom foot ACL injury mechanism, and strategies to avoid high-risk positions as well as effective reaction strategies.

The two seasons before the intervention season served as historical controls, during which area employees had sustained an average of 51 serious ACL sprains per season. During the intervention season, employees sustained 16 serious ACL sprains (6 in the untrained group and 10 in the trained group), a reduction of 62% compared with the normalised expected number of ACL injuries in the trained individuals of 26.6 (p<0.005).

### Isolated strengthening and conditioning

Cahill and Griffith looked at the effect of incorporating weight training into preseason conditioning for high school American football teams. Over the 4 years of the study they noted a reduction in reported knee injuries and knee injuries requiring surgery in the intervention group.

### Isolated proprioceptive training

In a study of the effect of isolated proprioceptive training on the risk of ACL injuries in soccer players, Caraffa et al. conducted a non-randomised prospective study of 600 semi-professional and amateur soccer players in Umbria and Marche in Italy; 20 teams (10 amateur and 10 semi-professional) underwent proprioceptive preseason training in addition to their regular training session (group A) and 20 teams (10 amateur and 10 semi-professional) continued training in their usual fashion (group B). The intervention group (group A) was subjected to a five phase progressive balance training programme consisting of: no balance board; rectangular balance board; round balance board; combination (rectangular/round); and a BAPS board (Camp Jackson, Michigan, USA). The duration/frequency was 20 min/day for 2–6 days/week including a minimum of 3 times per week during the season. The groups were followed for 3 years and all players with a potential knee injury were evaluated; 10 arthroscopically confirmed ACL injuries occurred over the three seasons (0.15 ACL injuries/team/season) in group A compared with 70 such injuries (1.15 ACL injuries/team/season) in group B (p<0.001). Unfortunately, no differentiation was made between contact and non-contact ACL injuries.

### Neuromuscular training

#### Technique

Several studies have used a neuromuscular training programme for injury prevention. Henning implemented a prevention study in two NCAA Division I female basketball programmes over the course of 8 years. He proposed that the increased rate of ACL injury in female athletes was primarily functional and was related to knee position and muscle action during dynamic movement. In knee extension the quadriceps exerts a significant anterior translational force on the tibia, thus imparting a shear force on the ACL. Conversely, as the knee moves into flexion, the anterior translational force on the tibia is decreased, thereby decreasing the torque on the ACL secondary to the contraction of the hamstrings. To decrease the risk of ACL injury, Henning proposed that the athletes cut, land and decelerate with knee and hip flexion. In addition, he proposed a rounded cut manoeuvre instead of a sharp or more acute angle during the cut cycle. He also proposed that a one-step stop deceleration pattern should be avoided and replaced with a three-step quick stop. This intervention programme was geared at changing player technique—stressing knee flexion upon landing, using accelerated rounded turns and deceleration with a multi-step stop. This protocol was completed on the basketball court without any additional equipment requirements. The intervention group had an 89% reduction in the rate of occurrence of ACL injuries. Sadly, Dr Henning’s passing in 1991 prevented the publication of this research. However, it served as the crucial foundation to numerous prevention programmes that followed.

#### Proprioception and strengthening

Henning’s concept of athletic modulation has been widely accepted. Wedderkopp et al. tested a programme including functional strengthening and balance training (use of an ankle disc for 10–15 min at all practice sessions). Teams were randomised into two groups with 11 teams in the intervention group (N = 111) and 11 in the control group (N = 126). The group using the ankle disc incurred 14 injuries compared with 66 injuries in the control group (p<0.01). The intervention...
group had a lower rate of injury during practice (0.34/1000 h vs 1.17/1000 h, p<0.05) and games (4.63/1000 h vs 23.38/1000 h, p<0.01). The intervention group suffered two knee injuries while the control group incurred eight knee injuries. No data specific to ACL injury were provided.

Irmischer et al10 developed the Knee Ligament Injury Prevention (KLIP) programme involving 15 min of strengthening and plyometric activities for female high school soccer, volleyball and basketball players. In the first season of a 2-year non-randomised prospective study, 43 schools participated in the programme (17 basketball (N = 191); 11 soccer (N = 189); 15 volleyball (N = 197)) and 69 schools served as the control group (28 basketball (N = 519); 14 soccer (N = 244); 27 volleyball (N = 299)). The study design included a training session for the coaches and athletic trainers and weekly compliance checks for athlete participation for both games and practices. There were no significant differences between the two groups after one season; three arthroscopically confirmed ACL injuries in the intervention group (incidence rate 0.167) vs four in the control group (incidence rate 0.078). Anecdotally, there were no non-contact ACL injuries in the soccer and volleyball players in the intervention group, with all of the injuries in the intervention group occurring in basketball players. Possible explanations for the lack of impact include the abridged duration of this intervention programme (9 weeks) and the fact that the programme was conducted after training. Neuromuscular fatigue at the end of training may directly affect the biomechanical technique of the athlete and limit any potential protective benefit of ACL injury prevention programmes.

Varied training
Other studies have incorporated additional dimensions of neuromuscular training into ACL prevention programmes. The Cincinnati Sportsmetric includes flexibility, strengthening (through weight training) and plyometric activities over 60–90 min. Hewett et al35 studied the effect of this programme on the incidence of knee injury in high school aged soccer, volleyball and basketball athletes. Forty-three teams (N = 1265 athletes) including 15 female teams (N = 366) implemented the programme; 15 additional female teams (N = 465) served as same-sex untrained controls and 13 male sports teams (N = 454) served as the male control group. Coaches and trainers implemented the programme based on a videotape and manual. The programme was performed 3 days/week on alternate days. Seventy percent of the intervention athletes (248/366) completed the entire 6-week programme and the remainder completed at least 4 weeks of training. The incidence of serious knee injuries (N = 14) in the female control group was 0.43/1000 player exposures compared with 0.12 in the female intervention group (p = 0.05) and 0.09 in the male control group. The intervention group also had a lower rate of non-contact injuries (p = 0.01) and non-contact ACL injuries (p = 0.05). The incidence of non-contact knee injury was 0.35/1000 player exposures in the control group compared with 0 in the intervention group and 0.05 in the male control group.

ACL injuries have also been problematic for European team handball players. Myklebust et al35 conducted a non-randomised prospective study among 900 division I–III competitive female handball players over a 5-year period in Norway. The control group comprised 60 teams (N = 942 players in 1998–9 season), and 58 teams (N = 855 in 1999–2000) and 52 teams (N = 850 in the 2000–1 season) formed the intervention group. The intervention consisted of a 15 min programme focused on landing, cutting and planting technique with 5 min spent on each of three exercise components (floor, balance mat and wobble board). The programme lasted 5–7 weeks with different exercises introduced each week. It was performed three times per week during the first 5–7 weeks and then once a week during the season. A physical therapist was designated to each team to assess compliance during the second intervention season (2000–1). Special equipment included an instructional videotape, a poster delineating the tasks to be completed, six balance mats and six balance boards. Teams were required to conduct a minimum of 15 training sessions over the 5–7-week period with >75% player participation. Only 15 (26%) of the 58 teams from the second season and 15 (29%) of the 52 teams from the third season completed the necessary number of sessions, although compliance was higher among the elite division teams (42% and 50%, respectively). Overall, there were 29 ACL injuries during the control season, 23 injuries during the first intervention season (odds ratio 0.87; CI 0.50 to 1.52; p = 0.62) and 17 injuries during the second intervention season (odds ratio 0.64; CI 0.35 to 1.18; p = 0.15). However, during the second intervention season, 14 ACL injuries (2.2%) occurred in players from the control group compared with 5 (1.1%) in players who completed the intervention (p = 0.31). In the elite division alone, 4 ACL injuries (8.9%) occurred in players from control teams compared with 1 ACL injury (0.6%) in those who completed the intervention (p = 0.0134). Thus, there was a reduction in the total number of non-contact ACL injuries from 18 in the control season to 7 during the second intervention season (p = 0.04). This intervention included elements of plyometric activities, proprioception and agility, but did not include any elements of strength training. Limitations of the study include non-randomisation of the subjects, insufficient power and control data that were collected during an earlier season. Strengths of the study include measures of compliance by a medical clinician and the use of an educational videotape and poster. The study suggests that the inclusion of a neuromuscular balance-based training programme may impart some protective benefit to the ACL.

Comprehensive training
Olsen et al35 studied a programme designed to prevent lower limb injury in youth team handball. One hundred and twenty European team handball clubs (intervention group: 61 teams, 958 players; control group: 59 teams, 879 players) participated in an 8-month intervention programme that consisted of four sets of exercise lasting 15–20 min. The training consisted of warm-up exercises (jogging, backward running, forward running, sideways running and speed work), technique (plant, cut and jump shot landing), balance (passing, squats, bouncing, perturbation) and strength and power (squats, bounding, jumps, hamstrings). Each club was instructed on how to perform the programme and was issued a training handbook, five wobble boards and five balance mats. The programme focused on proper biomechanics during landing, core stability and feedback on technique between paired team members. The intervention teams consisted of boys and girls aged 16–17 years who completed 15 consecutive training sessions at the start of the season followed by one training session per week for the remainder of the season. Sixty six lower limb injuries (6.9% of players) were reported in the intervention group compared with 115 (13.1%) in the control group (relative risk 0.51; 95% CI 0.36 to 0.73; p<0.001); 19 acute knee injuries (2.0%) occurred in the intervention group compared with 38 (4.3%) in the control.
group (relative risk 0.45; 95% CI 0.25 to 0.81; p = 0.007); and 3 knee ligament injuries were reported in the intervention group compared with 14 in the control group (relative risk 0.20; 95% CI 0.06 to 0.70, p = 0.01). All 3 knee ligament injuries in the intervention group were ACL injuries while 10 of the 14 reported knee injuries in the control group were ACL injuries; no data were provided on ACL injuries alone. A compliance rate of 87% was reported. The strength of the team handball programme is that it is a warm-up programme which makes it easier to be performed at every training session. This may be essential for long-term success of such a programme. The intervention included strength, flexibility, agility, plyometric and proprioceptive activities to address the deficits most commonly found in female athletes.

Many of these intervention programmes require special equipment, specialised training, or significant time commitment. In 1999 the ACL “PEP Program: Prevent injury and Enhance Performance” was developed in Santa Monica, California. This prevention programme consists of warm-up, stretching, strengthening, plyometrics and sport-specific activities to address potential deficits in the strength and coordination of the stabilising muscles around the knee joint. It was designed as an alternative warm-up so that the desired activities could be performed on the field during practice without specialised equipment for ease of implementation. The programme consists of an educational videotape/DVD that demonstrates the proper and improper biomechanical technique for each prescribed therapeutic exercise. An entire team can complete the 19 components in less than 20 min.

An early non-randomised study among highly competitive 14–18-year-old female club soccer players using the programme showed promising results. During the first year of the study (2000) 1041 female club soccer players (52 teams) performed the PEP programme and 1902 players (95 teams) served as age- and skill-matched controls. In the intervention group there were 2 ACL tears (0.2 ACL injuries/athletic exposure (AE)) compared with 52 ACL tears (1.7 ACL injuries/AE) in the control group, a decrease of 88% in ACL ligament injury. In year 2 of the study (2001) 4 ACL tears were reported in the intervention group (incidence rate 0.47 injuries/AE) compared with 35 in the control group (incidence rate 1.8 injuries/AE). This corresponds to an overall reduction of 74% in ACL tears in the intervention group compared with an age- and skill-matched control group in year 2. The limitations of this study include non-randomisation of the subjects, no consistent direct oversight of the intervention and compliance measurements that were only completed in a small subset of intervention teams.

The strengths of the PEP Program include the fact that it is an on-field warm-up programme that requires only traditional soccer equipment (cones and soccer ball). It is done 2–3 times a week over the course of the 12-week soccer season and is 20 min in duration. It includes progressive strength, flexibility, agility, plyometric and proprioceptive activities to address the deficits most commonly demonstrated in female athletes. Deceleration patterns are addressed, stressing the multi-step deceleration pattern, and proper landing technique is encouraged with knee and hip flexion while landing on the ball of the foot and avoiding genu valgum by using the abductors and lateral hip musculature. In addition, since the programme is designed as a warm-up, compliance rates are higher and the element of neuromuscular fatigue does not affect the performance of the therapeutic exercises.

This study was followed by a randomised controlled trial using the PEP Program in Division I NCAA women’s soccer teams in the 2002 Fall season. Sixty-one teams (N = 1429 athletes) completed the study (35 control teams (N = 854 athletes) and 26 intervention teams (N = 575 athletes)). No significant differences were seen between intervention and control athletes with regard to age, height, weight or history of past ACL injuries. After using the PEP Program during one season there were 7 ACL injuries in the intervention athletes (rate 0.14) and 18 in control athletes (rate 0.25; p = 0.15). No ACL injuries were reported in intervention athletes during practices compared with 6 in control athletes (rate 0.10; p = 0.01). During games the difference between the intervention and control groups was non-significant (7 vs 12; p = 0.76). Non-contact ACL injuries occurred at over three times the rate in control athletes (n = 10; rate 0.14) compared with intervention athletes (n = 2; rate 0.04; p = 0.06). Control athletes with a prior history of ACL injury suffered a recurrence five times more frequently than the intervention group (0.10 vs 0.02; p = 0.06); this difference reached significance when limited to non-contact ACL injuries during the season (0.06 vs 0.00; p < 0.05). There was a significant difference in the rate of ACL injuries in the second half of the season (weeks 6–11) between the intervention group (0.00) and the control group (0.18; p < 0.05). This supports the notion that it takes approximately 6–8 weeks for a biomechanical intervention programme to impart a neuromuscular effect.

Overall, these studies provide evidence that prevention training programmes can reduce the risk of ACL injury. This has been shown in male and female athletes from various sports and across different age groups. Nevertheless, a number of important issues remain.

**Programme specifics**

Practically, there is a cost-benefit analysis that needs to be considered before initiating an injury prevention programme on a large scale.

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**Figure 3** Single leg squat. The athlete should maintain a straight line through the hip, knee and toe. She should keep a horizontal orientation of the hips and avoid a pelvic tilt during one-legged squat balance exercises. The athlete should be encouraged to reach deep knee flexion when performing this drill.
First, what equipment is necessary and at what cost? Extensive and more expensive equipment is necessary for programmes such as the Frappier Acceleration Program, the Cincinnati Sportsmetric Program and the various programmes using some form of balance board. Other successful programmes such as PEP and the Henning programme can be performed with minimal resources.

Second, what is the minimal time commitment needed to provide adequate protection? What is the minimum duration of an injury prevention programme or does it need to be continued, perhaps at a lesser frequency throughout the course of the season? When initiating a neuromuscular intervention programme, it takes approximately 4–6 weeks to impart a benefit to the athlete. Most of the programmes studied to date have a relatively intense start-up period for 4–6 weeks followed by less frequent and, in some cases, no additional training. Maintenance of the programme in a routine manner as part of a warm-up and ongoing training is crucial to successful reduction of injury.

**Timing of intervention**

Ideally, these prevention programmes should be introduced as early as possible in the training period. In some sports this would be at the age of 6–10 years.

**Effect on performance**

One additional advantage of prevention programmes is that, properly executed, they can serve to enhance performance as well as prevent injury. These benefits include increased vertical jump, improved control of dynamic load of the knee, improved balance and increased hamstring strength, power and peak torque.

**Summary of prevention programmes**

- Based on these studies, we know that there can be a quantifiable reduction in the risk of ACL for athletes, particularly women, who complete a well-designed injury prevention programme.
- Most of these programmes attempt to alter dynamic loading of the tibiofemoral joint through neuromuscular and proprioceptive training.
- An emphasis is placed on proper landing technique; landing softly on the forefoot and rolling back to the rearfoot, engaging knee and hip flexion upon landing. Two-feet landing is encouraged where possible.
- When cutting manoeuvres, athletes should avoid excessive dynamic valgus of the knee upon landing and squatting; they should aim to achieve the “knee over toe position”.
- Intervention programmes have focused on increasing hamstring, gluteus medius and hip abductor strength, and addressing proper deceleration techniques.
- Successful implementation of these programmes requires the collaboration of governing bodies, sports scientists, physicians, coaches, parents and athletes.

**Important factors for a successful prevention programme**

- The programme should include strength and power exercises, neuromuscular training, plyometrics and agility exercises.
- Design as a regular warm-up programme increases adherence.
- Focus should be on performance of the hip-knee-foot line and “kissing knees” should be avoided (excessive valgus strain).
Maintenance and compliance of prevention programmes before, during and after the sports participation season are essential to minimise injuries.

The drop vertical jump test should be used to identify players at risk (fig 4).

The programme must be well received by coaches and players to be successful.

Evaluation of success or failure of a prevention programme requires large numbers of athletes and injuries.

OVERALL SUMMARY AND FUTURE DIRECTIONS

There is consensus in the literature that female athletes have a greater risk of incurring an ACL injury than male athletes when they compete in the same sport at the same level of competition. However, most studies have focused on the prevalence of ACL injuries associated with high-risk sports; only a limited number have calculated the incidence of ACL injury based on time at risk and compared male and female athletes competing in similar activities at the same level of competition.

There appears to be mounting evidence that women have a significantly greater risk of ACL injury during the preovulatory phase of the menstrual cycle than during the postovulatory phase. While it remains unclear whether oestriol and progesterone act directly on the ACL in women and increase the likelihood that a subject will sustain an injury, other hormones associated with the menstrual cycle may modulate the risk of injury. Alternatively, hormones may act on structures other then the ACL. Athletes with a decreased intercondylar notch width, as measured radiographically on a standard notch view, have an increased risk of incurring a non-contact ACL injury.

Little is known about how lower leg alignment variables are related to the likelihood of suffering a knee ligament injury. Anatomical risk factors may not be easy to correct; however, they are important to understand if subjects at increased risk of incurring an ACL injury are to be identified.

Female athletes who develop an increased knee abduction moment (valgus intersegmental torque) during impact on landing have an increased risk of ACL injury. Female athletes have muscle activation patterns in which the quadriceps predominates and decreased knee stiffness appears to occur. The relative increase in knee stiffness in response to anterior-directed perturbation of the knee is much greater in men than in women. More research is needed into the neuromuscular risk factors related to ACL injury.

Very little is known about the effect of sport-specific factors (such as rules, referees and coaching), meteorological conditions (such as the traction at the shoe-surface interface), playing surfaces and protective equipment on the risk of suffering an ACL injury. These potential risk factors merit further investigation.

Little is known about the effect of age, athleticism, skill level, psychological characteristics and previous knee injury as risk factors for ACL injury.

There is a quantifiable reduction in the risk of ACL in athletes, particularly women, who complete well-designed injury prevention programmes. Proper neuromuscular training can decrease peak landing forces. Training will significantly enhanced hamstring strength and power, and reduce hamstring to quadriceps and side-to-side strength imbalances. It is also important to increase gluteus medius and hip abductor strength and to address proper deceleration techniques. Most of these programmes attempt to alter dynamic loading of the tibiofemoral joint through neuromuscular and proprioceptive training. Emphasis is placed on proper landing technique—landing softly on the forefoot and rolling back to the rearfoot, engaging knee and hip flexion upon landing; two-feet landing instead of one feet should be used if possible. In cutting manoeuvres, excessive dynamic valgus of the knee upon landing and squatting should be avoided, focusing on the “knee over toe position”.

Successful implementation of these programmes requires the collaboration of governing bodies, sport scientists, physicians, coaches, parents and athletes. Everybody can participate in the fight to prevent the ACL injury, especially in young female athletes. Increased and substantial support from the sports medicine community as well as from the sporting world is required to ensure success in this battle so that ACL injuries are eradicated, or at least substantially reduced.

Competing interests: None.

REFERENCES


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