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Sex comparison of familial predisposition to anterior cruciate ligament injury

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Abstract

Purpose—In an effort to identify risk factors for anterior cruciate ligament (ACL) injury, many potential risk factors have been proposed, including familial predisposition. However, no study has evaluated familial predisposition in male or females separately. The purpose of this study was to determine whether a familial predisposition to ACL injury exists in both males and females.

Methods—One hundred and twenty (78 males and 42 females) patients who had undergone surgical ACL reconstruction were recruited as the ACL group, and 107 patients (67 males and 40 females) that had undergone arthroscopic partial menisectomy, with no previous history of ACL injury, were recruited as the referent control group. A familial ACL injury and subject particulars questionnaire was completed.

Results—When all subjects were combined, the ACL group (20.0 %, 24 of 120) did not demonstrate a higher familial (first-degree relative) prevalence (n.s.) of ACL injury compared to the referent control group (15.0 %; 16 of 107 patients). When the data were stratified by sex, the male ACL group (19.2 %, 15 of 78) demonstrated a significantly higher familial (first-degree relative) prevalence ($P = 0.02$) of ACL injury compared to the male referent control group (7.5 %; 5 of 67 patients). There were no differences among the females (n.s.).

Discussion—The results of this study show that male patients with ACL tears are more likely to have a first-degree relative with an ACL tear compared to male referent control subjects. Future research is warranted to better delineate sex-specific risk factors for ACL injuries could help guide intervention programs aimed at preventative treatment strategies, especially in high-risk families.

Keywords

Genetics and sport; Genetics and neuromuscular performance; Family history of injury; Injury prevention

Introduction

Anterior cruciate ligament (ACL) rupture is a severe knee injury, leading to functional instability in the short term and to early degenerative joint disease in the long term. Although ACL reconstructive procedures are available, the injury is painful, costly and can be debilitating. The high physical, mental, emotional and economic cost of these injuries has prompted research into risk factors and preventative strategies. ACL rupture is a multifactorial injury with several intrinsic and extrinsic risk factors. Intrinsic risk factors include anatomical, hormonal, neuromuscular and genetic factors. Among the genetic risk factors, research studies have shown familial predispositions to ACL ruptures, as well as specific genetics sequence variants. One suggested intrinsic factor, femoral notch width, has been investigated in detail [5, 10]. Smaller notches have been associated with increased rate of ACL injury [15]. Lambert touched upon the possibility of familial predisposition of ACL injury due to femoral notch configuration. Specifically, it was proposed that a narrow notch and ACL rupture has been traced in successive generations of several families, suggesting that specific notch configuration may be heritable [17]. Anderson et al. [6] alluded to familial predisposition in their analysis of intercondylar notch by computed tomography. Notch dimensions/configuration and ligamentous laxity were compared among patients with bilateral ACL tears, unilateral ACL tears and normal knees. Although certain notch parameters were found to be statistically significant for ACL tear, families of those with bilateral and unilateral ACL tears had no greater incidence of knee injuries than the families of those with normal knees. Absent from this study were any specific methods that described how familial incidence was assessed. Bilateral ACL injuries and associated intercondylar notch stenosis were studied by Souryal et al. [22]. A complete medical and family history was recorded at the time of follow-up to evaluate for possible predisposing factors for ACL injury. Although the study suggested that the width of the intercondylar notch might predispose a person to an ACL tear, no significant differences in medical or family history were recorded.

Harner et al. [12] assessed for possible predisposing factors, including a familial predisposition, in patients with bilateral non-contact ACL ruptures. This was the first study to specifically assess a familial predisposition to ACL injury. Patients with bilateral ACL injuries had a significantly greater number of immediate-family members with ACL rupture, when compared to non-ACL-injured controls. More recently, Flynn et al. [11] reported similar findings. When the analysis was limited to first-degree relatives, participants with an ACL rupture were greater than twice as likely to have a first-degree relative with an ACL tear compared to participants without an ACL tear [11]. If familial predispositions to ACL injury are indicated, clinicians may be better positioned to counsel patients who participate in high-risk sports and families with injury history to initiate targeted preventative strategies. Since it remains unknown whether a familial predisposition towards ACL ruptures is an inherited trait in both male and females, the objective of this study was to determine whether a familial predisposition to ACL injury exists in both males and females. Prior work indicates specific genes such as *COL5A1* and *COL12A1* were only found to be associated with risk of ACL ruptures in females [20]. Therefore, we hypothesized that a familial disposition to ACL injury would be indicated in female athletes with no similar associations in males.

Materials and methods

Two hundred and twenty-seven patients were recruited for this retrospective case–control study. One hundred and twenty patients (78 males and 42 females) had undergone surgical reconstruction of a torn ACL (ACL group). One hundred and seven patients (67 males and 40 females) that had undergone arthroscopic partial meniscectomy, with no previous history of ACL injury, were recruited as the referent control group. The ACL and referent control groups were matched for sex (ACL, 65.0 % male; referent control 62.6 % male; $P = 0.709$) and ethnicity (ACL, 95.0 % Caucasian; referent control 92.5 % Caucasian; n.s.). The referent control group was significantly older than the ACL group (ACL, 27.3 ± 0.7 years; referent control, 31.8 ± 0.6 years; $P < 0.001$) at the time of surgery.

Inclusion criteria included the following: surgical reconstruction of ACL tear (ACL group) or arthroscopic surgery for torn meniscus without a previous history of ACL injury (referent control group), age between 18 and 40, male and female. All techniques of ACL reconstruction (i.e. bone–patellar tendon–bone autograft, hamstrings autograft, allograft) were included and any patient who was identified for the meniscectomy group (referent control group), but during the telephonic interview, it was discovered that they had since had an ACL tear which was reconstructed, were subsequently moved to the ACL group. Exclusion criteria included subjects with no information on biological family members (i.e. adoption), any neurological or systemic disease affecting the lower extremity, and minors (<18 years) or patients 40 years and older.

All participants were contacted retrospectively from a private practice database and requested to partake in this study. All participants gave informed consent and completed a short telephonic questionnaire (Athletic Knee Injury Family History) to obtain first-degree family ACL injury history and diagnosis. The questionnaire also determined demographic data regarding the affected relative including sex, age at time of injury, cause of injury, level of play and race/ethnicity. Details about the participation requirements and study benefits were explained to the subject at the time of questionnaire completion. This study was approved by the Schulman Associates Institutional Review Board.

Statistical analysis

Data were analysed using Graphpad version 5 (Graphpad Software, San Diego, California, USA) statistical programs. A one-way analysis of variance (ANOVA) was used to determine any significant difference between the characteristics of the ACL and referent control group. A chi-square (χ^2) analysis or Fisher's exact test was used to analyse any differences in the prevalence of having a first-degree relative with an ACL injury, as well as other categorical data between the groups. Our a priori hypothesis was that the risk of ACL injury is increased within individuals with a first-degree relative with an ACL injury. We therefore performed one-tail Fischer's exact or chi-square tests, where appropriate. Significance was accepted when $P < 0.05$.

Results

The 227 study subjects consisted of 120 patients in the ACL group (78 males and 42 females) and 107 patients in the referent control group (67 males and 40 females). When all subjects were combined, the ACL group (20.0 %, 24 of 120) did not demonstrate a higher familial (first-degree relative) prevalence (n.s.) of ACL injury compared to the referent control group (15.0 %; 16 of 107 patients).

When the data were stratified by sex, the male ACL group (19.2 %, 15 of 78) demonstrated a significantly higher familial (first-degree relative) prevalence ($P = 0.020$) of ACL injury compared to the male referent control group (7.5 %; 5 of 67 patients). The prevalence of a familial predisposition was not significantly different (n.s.) between the female ACL group (21.4 %, 9 of 42) and the female referent control group (27.5 %, 11 of 40).

Discussion

The primary finding of this study was that males with a first-degree relative with an ACL injury were at increased risk of an ACL injury. Interestingly, this association was not found when only female patients or when male and female patients were collectively analysed. The primary findings are in agreement with the two previous studies investigating a familial predisposition [11, 12]. In contrast to the previous two studies, the current study was not able to show significant differences in familial predisposition to ACL rupture when males and females were collectively analysed.

The two most recent case–control studies that focused on familial predisposition to non-contact ACL tears showed that there is likely a genetic component to this devastating injury. Harner et al. [12] discovered a higher incidence of ACL tears in the immediate-family member group (35 %) than that of a control group (4 %) in a matched case–control design that utilized a medical history questionnaire. In 2005, Flynn et al. [11] studied a larger case–control group of 342 patients including 171 patients with ACL tears and reported that the patients with an ACL injury were twice as likely to have a relative with an ACL tear compared with the control group patients that did not have a tear.

The prevalence of ACL injury among first-degree relatives in the current study was 19.2 % in the male ACL group and 7.5 % in the male referent control group. Among the female patients, the prevalence among ACL injured was 21.4 % and among the referent control group 27.5 %. There are specific genetic variants, which have been implicated in the aetiology of ACL ruptures risk of ACL ruptures. The *COL1A1* and *MMP12* genes have been shown to associate with risk within all participants, whereas the *COL5A1* and *COL12A1* genes have been shown to associate with risk of ACL ruptures only in females [20]. Therefore, we hypothesize a stronger familial relationship with ACL injury in the female cohort. Our hypothesis was not supported as the female control group demonstrated a high prevalence of familial ACL injury and may explain why no significance was found within this group. Further research is required to evaluate the hypothesis whether a familial predisposition to ACL is a significant risk factor among females.

Multiple studies and recent focus have highlighted the anthropometric differences between male and female athletes as they relate to the ACL injury incidence and prevalence. In 1997, Bjordal et al. [8] examined the difference between the two sexes in competitive soccer players in Norway, discovering that females have a significantly higher risk of ACL injury than males. Anderson et al. correlated intercondylar notch measurements, quadriceps strength and ACL size in 100 matched high school athletes in 2001. These authors concluded that several interrelated intrinsic factors, including stiffness, strength and the size of the ACL, put increasing stress on the ACL and can therefore be partly responsible for the discrepancy of ACL tears between sexes [5]. This heritable trait of notch size was further investigated in 2005 by Chandrashekar et al. in a cadaveric laboratory study. No significant difference in mass density was appreciated between male and female groups; however, the female ACLs were smaller in size. Therefore, the authors concluded that the female ACL smaller size may be a factor contributing to the higher rupture rate in this population as compared to males [10]. Chandrashekar et al. [9] discovered that there was a significantly lower modulus of elasticity (22 %), lower strain at failure (8 %) and lower stress at failure (14 %) in the female subjects as compared to male. It is reported that females have a three–sixfold higher risk of ACL injury rate than their male counterparts who play the same sports at similar levels [1, 7]. However, due to the large numbers of male athletes participating in sports, there are likely equal to or similar overall prevalence of ACL injury worldwide. Due to the current results, more research may be warranted in male athletes that are focused on inheritable family traits.

Ligamentous laxity and increased hyperextension which may be related to family predispositions are related to increased incidence in non-contact ACL injuries in female athletes [18, 21]. A recent report evaluated twin female siblings compared to a large control cohort of similar age and sport participation to investigate potential familial predisposition for intrinsic neuromuscular and anatomical risk factors to injury. The prospective data from the twins who went on to sustain ACL tears indicated increased knee abduction angles, increased knee abduction range of motion and decreased knee flexion when compared to the uninjured controls [13]. It has been purported that neuromuscular factors which may be more related to training exposure (or lack thereof) in females may underlie increased risk of ACL injury in female athletes [4, 14]. These differences in neuromuscular development might have contributed to the limited familial relationship for ACL injury in females that was indicated in the male participants. Future work to evaluate the familial relationships for neuromuscular control and their contributions to increased ACL injury risk are warranted. Understanding the multiple patient risk factors, specifically sex-specific risk factors for ACL injuries in male athletes could help guide overcome their familial predisposition to ACL injury. Counselling and appropriate pre-participation screening/targeted training may be indicated in male patients who participate in high-risk sports and have a first-degree relative with a prior ACL injury.

ACL injuries are one of the most common severe injuries and are often associated with the greatest time lost in sport in athletics. Female athletes demonstrate increased incidence rates of ACL injury compared to their male counterparts playing similar sports. Based on this discrepancy, investigations into risk and preventative strategies most often focus on females. While significant advancements the evidence related to preventative strategies in females [19], the relative prevalence of ACL injured likely equal or exceeds the in total magnitude of numbers reported in female athletes [16]. A recent systematic review focused to synthesize the existing evidence on risk factors and prevention programs for ACL injury in male athletes reported that the current state of knowledge related to risk factors, especially for neuromuscular and biomechanical factors, is deficient in the male athlete. Likewise, the number of studies applying prevention programs to decrease ACL injuries is clearly insufficient to draw conclusions intervention strategies to prevent ACL injuries [2, 3].

There are a number of limitations to the current study. The exact mechanism of ACL injury was unknown among the ACL injury group, as well as among the reported injuries to first-degree relatives. The injuries to relatives were also not clinically or surgically diagnosed and relied on patient reporting. It is also unknown whether the number of first-degree relatives, or exposure to sporting activities were matched between the ACL and referent control groups. The current study used patients, which had undergone meniscal injuries as controls.

The group of female patients who had undergone meniscal surgery demonstrated a high prevalence of ACL rupture among their first-degree relatives. The exact reason why the incidence in this group may have been higher than the general population remains unknown, but may be a limitation of the study.

Conclusions

To our knowledge, this is the first study that has identified a possible risk factor for ACL tears in males that is higher than in females. The results of this study indicate that male athletes with a first-degree relative who have sustained an ACL tear are at higher risk of an ACL tear themselves than the average population. This could be explained as males may have a stronger familial genetic predisposition to increased familial ACL injury risk, while females may be more susceptible to other risk factors such as developmental neuromuscular control deficits. Understanding the multiple patient risk factors, specifically sex-specific risk factors for ACL injuries in male athletes, could help guide strategies to overcome their familial predisposition to ACL injury.

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