Brief Report

Anterior knee pain following anterior cruciate ligament reconstruction does not increase the risk of patellofemoral osteoarthritis at 15 and 20 years follow-up

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RUNNING TITLE
Patellofemoral pain and osteoarthritis

ABSTRACT

Objective. To prospectively evaluate the relationship between the presence or persistence of anterior knee pain during the first 2-years following anterior cruciate ligament reconstruction (ACLR) and patellofemoral osteoarthritis at 15- and 20-years.

Design. This study was ancillary to a long-term prospective cohort study of 221 participants following bone-patellar tendon-bone ACLR. Anterior knee pain was assessed at 1- and 2-years post-ACLR using part of the Cincinnati knee score with an additional pain location question (persistence defined as presence at both follow-ups). Radiographic patellofemoral osteoarthritis (definite patellofemoral osteophyte) and symptomatic patellofemoral osteoarthritis (patellofemoral osteophyte, with knee pain during past four weeks) was assessed at 15- and 20-year follow-up. We used generalised linear models with Poisson regression to assess the relationship between anterior knee pain and patellofemoral osteoarthritis.

Results. Of the 181 participants (82%) who were assessed at 15-years post-ACLR (age 39±9 years; 42% female), 36 (24%) and 33 (22%) had anterior knee pain at 1- and 2-years, respectively, while 14 (8%) reported persistent anterior knee pain. Radiographic and symptomatic patellofemoral osteoarthritis was observed at 15-years in 130 (72%) and 70 (39%) participants, respectively, and at 20-years in 115 (80%) and 60 (42%) participants, respectively. Neither the presence nor persistence of anterior knee pain at 1- and/or 2-years post-ACLR was associated with significantly higher risk of radiographic or symptomatic patellofemoral osteoarthritis at 15- or 20-years (risk ratios <2.1).

Conclusions. Although anterior knee pain and patellofemoral osteoarthritis were prevalent, anterior knee pain does not appear to be associated with long-term patellofemoral osteoarthritis following ACLR.

Keywords: anterior cruciate ligament, anterior knee pain, patellofemoral joint, osteoarthritis

The patellofemoral joint is increasingly recognized as a key contributor to knee osteoarthritis (OA) and is strongly associated with pain[1]. There is speculation that a history of anterior knee pain (AKP) (i.e., patellofemoral pain) may be an indicator of early patellofemoral degeneration and that such symptoms precede the development of patellofemoral OA (PFOA)[2,3]. Individuals undergoing arthroplasty for isolated PFOA were more than twice as likely to retrospectively report having had AKP during adolescence than patients undergoing arthroplasty for tibiofemoral OA (TFOA)[3]. However, no studies have prospectively evaluated individuals with AKP through to PFOA development (or non-development).

AKP and PFOA are particularly common and troublesome complications in young adults after anterior cruciate ligament reconstruction (ACLR), irrespective of graft type[4,5]. AKP occurs in 30-50% of patients 1-2 years following ACLR[4,6], while approximately half of all patients suffer from radiographic PFOA ≥10-years post-ACLR[5]. If AKP is prospectively found to increase the risk of longer-term PFOA, management strategies aimed to reduce the PFOA risk may be targeted at those with AKP. Therefore, the aim of the current study was to determine whether the presence or persistence of AKP at 1- and 2-years post-ACLR was associated with increased risk of radiographic and/or symptomatic PFOA at 15- or 20-years post-ACLR. Based on previous retrospective data, we hypothesized that the presence and persistence of AKP at 1- and 2-years post-ACLR would be associated with increased risk of radiographic and symptomatic PFOA at 15- and 20-years.

METHODS

Participants

This study was ancillary to a prospective evaluation of knee function and OA post-ACLR in Norway. 221 subjects who underwent ACLR with a bone-patellar-tendon-bone autograft[7]

were consecutively recruited between 1990 and 1997 and have been prospectively followed at 6-months, 1-year, 2-years, 15-years, and 20-years post-ACLR. Initial inclusion criteria were: aged 14-50-years at time of surgery, and no other major ligament/bone injuries in either lower-extremity in the year prior to ACLR.

Meniscal injuries requiring treatment underwent partial resection or suturing as indicated arthroscopically. Chondral lesions were shaved and loose edges removed according to surgical assessment. All participants completed similar postoperative rehabilitation, including early weight-bearing, with an emphasis on neuromuscular and strength training to re-establish knee function[7].

Two-year symptomatic and functional outcomes have been published on 155 participants[7,8], and 15- and 20-year postoperative results for knee symptoms, function and OA have recently been published on 181 and 144 participants, respectively[9,10]. The Regional Ethical Committee approved the study, and all subjects signed informed consent.

Assessment of anterior knee pain

Presence of AKP pain at the 1- and 2-year postoperative follow-ups was defined using the pain variable of the Cincinnati knee score (a patient-reported outcome assessing symptoms, function and sports activity) in addition to a question related to pain location. Specifically, AKP was considered present when participants responded less than the maximum pain-free score of 20-points on the pain variable of the Cincinnati score (i.e., participants reported at least intermittent pain during any activity or rest) when the pain was located in the anterior knee (i.e., patella). This definition has previously been used to report AKP prevalence 1- and 2-years post-ACLR[7].

Radiological examination

To assess patellofemoral abnormalities at 15- and 20-year follow-ups, bilateral standardized weight-bearing lateral and skyline radiographs were acquired with approximately 40° knee flexion in a specially designed frame. Radiographic PFOA was defined using the recently suggested Kellgren-Lawrence grade 2 cut-off modification (KL2/osteophyte) adapted for PFOA (i.e., definite osteophyte in patellofemoral compartment), as used in the 20-year follow-up of this cohort[10]. Radiographic assessment was performed by an experienced radiologist with established inter-rater reliability for Kellgren-Lawrence classification (κ 0.77)[9]. We also assessed symptomatic PFOA by asking the question: 'Have you had knee pain during the last 4-weeks?' Those who had both knee pain and a definite patellofemoral osteophyte in their ACLR knee were defined as having symptomatic PFOA (all other participants were defined as not having symptomatic PFOA and were included in the referent group for analyses). Radiographic and symptomatic tibiofemoral OA has also been evaluated at the 15- and 20-year follow-ups using posteroanterior radiographs and the same question regarding knee symptoms. TFOA prevalence and risk factors have been reported previously[9,10].

Other assessments

Body mass index (BMI) was calculated for all follow-ups (kg/m^2). Concomitant injuries assessed arthroscopically at the time of ACLR or sustained during the follow-up period were registered from the index surgical notes and by asking participants about additional injuries at 15- and 20-year follow-ups, respectively. Concomitant and additional injuries included meniscal/cartilage lesions, or MCL injuries (grade III). Participants were only classified as having isolated ACL injury if they had no concomitant or additional injuries for the entire follow-up period.

Statistical analysis

Descriptive statistics were used to describe frequencies of AKP and PFOA at each relevant follow-up. Generalised linear models with Poisson regression were used to assess whether the presence of AKP at 1- *or* 2-years post-ACLR, or persistence of AKP at both 1- *and* 2-years, was associated with an increased risk of radiographic and/or symptomatic PFOA at 15- or 20-years. Each analysis was adjusted for sex, age, BMI and combined vs. isolated injury at 15- or 20-year follow-up, respectively. Risk ratios and 95% confidence intervals (CIs) were calculated. A risk ratio >1.0 represents greater risk of PFOA in the presence (or persistence) of AKP. Risk ratios with 95%CIs not crossing 1.0 were considered statistically significant. Statistical analyses were completed with SPSS-V.20.

RESULTS

Of the 221 subjects who underwent ACLR with a bone-patellar-tendon-bone autograft, 181 (82%) and 142 (64%) participants were evaluated with radiographs at 15- and 20-year follow-up, respectively (Table 1). Reasons for loss to follow-up have been published previously[9,10]. AKP pain data was missing/incomplete at 1- and 2-year follow-up in 28 (15%) and 20 (11%) participants, respectively. Of the 130 participants with radiographic PFOA at the 15-year follow-up (Table 1), 110 (85%) had concomitant radiographic TFOA, while 20 (15%) had isolated radiographic PFOA. The prevalence of symptomatic PFOA was approximately half that of radiographic PFOA at both 15- and 20-year follow-up (Table 1). Thirty-six (24%) and 33 (20%) participants suffered from AKP at 1- and 2-years post-ACLR, respectively, while 14 (10%) reported persistent AKP (Table 1). Details of additional injuries in the 112 participants with concomitant pathology appear elsewhere[9].

TABLE ONE HERE

Neither the presence nor persistence of AKP at 1- and/or 2-years post-ACLR was associated with increased risk of radiographic or symptomatic PFOA at 15- or 20-years post-ACLR (Table 2). Persistent AKP was generally more strongly associated with an increased risk of PFOA (i.e., all RR>1.0), however, no statistically significant differences were observed (Table 2; Supplementary File 1).

TABLE TWO HERE

DISCUSSION

Anterior knee pain is one of the most common knee problems seen in sports injury clinics and is a well-established complication following ACLR[4]. Although many individuals with AKP have recurrent symptoms and are suspected to develop PFOA[2,3], the results of this prospective study with >140 participants show that neither the presence nor persistence of AKP within the first 2-years post-ACLR was associated with increased risk of radiographic or symptomatic PFOA at 15-20 years post-surgery.

The current study is the first, to our knowledge, to prospectively evaluate the relationship between AKP early post-ACLR (1- and 2-years) and development of PFOA (15-20 years post-ACLR). Although a relationship between idiopathic AKP and PFOA has been inferred based on similarities in impairments and previous retrospective study results[2], our prospective data do not support that the two entities are linked on a continuum post-ACLR. Our results contrast with the previous retrospective case-control study, which did report a link between PFOA and AKP in adolescence[3]. However, this retrospective study was limited by considerable recall bias (i.e., patients asked to recall symptoms from 50-years previously)[3]. Recent quantitative magnetic resonance imaging data found no difference in early PFOA

markers (i.e., cartilage composition) between young (23±6 years) patients with and without AKP[11]. Prospective studies are needed to longitudinally evaluate the relationship between idiopathic AKP and PFOA.

Anterior cruciate ligament reconstruction interrupts the extensor mechanism through harvest of the BPTB autograft. This surgical intervention alters patellofemoral alignment and kinematics, and results in a particularly high prevalence of AKP and early-onset PFOA (both approximately 50%) in young adults[5,6]. AKP post-ACLR may be a different entity to idiopathic AKP in knees without a history of acute injury or surgery, due to surgical incision and iatrogenic trauma to the extensor mechanism, persistent effusion, immobilization and marked quadriceps strength loss post-operatively[5]. Although approximately one-quarter of participants reported AKP at 1- and 2-years post-ACLR, only 10% suffered from persistent AKP at both follow-ups, suggesting considerable variability in the onset and resolution of symptoms post-surgery. Evaluation of post-operative AKP severity and duration may allow more specific patterns, or even phenotypes, of pain characteristics to be identified. Although our results show that AKP is not a precursor to PFOA post-ACLR, post-surgical AKP should still be targeted during rehabilitation programs as AKP post-ACLR is a frequent problem and has a significant burden on physical performance and quality-of-life[4].

PFOA following ACLR may also differ from its idiopathic counterpart. Following ACL injury and subsequent ACLR, the biomechanics of the knee joint are altered[12], with a typical post-operative gait pattern consisting of lower peak knee flexion angles, and tibial rotation offsets[13]. These changes potentially result in a change in loading to an area of the patellofemoral joint unaccustomed to load[5]. This may contrast the known biomechanical factors leading to idiopathic PFOA, which are mostly centered on patellofemoral malalignment, quadriceps and hip abductor weakness, and abnormal biomechanics[2].

The duration between AKP and PFOA assessment (i.e., 14-19 years) may have been too long to detect a specific link between the two entities, as other factors, such as meniscal pathology, altered knee biomechanics and impairments in knee range of motion and quadriceps strength are known to contribute to PFOA development post-ACLR[5]. However, 10+ years post-ACLR is generally required to enable detectable radiographic changes to develop in these young adults. While quadriceps strength, anterior knee laxity and hop test data were collected at the 1- and 2-year follow-up periods, these data were not included as covariates as there was no association with PFOA in this cohort[14]. There were few participants with isolated radiographic PFOA (15%). While the presence of concurrent TFOA may influence the relationship between AKP and PFOA, additionally adjusting the regression models for TFOA presence did not alter results. The general knee pain used to define symptomatic PFOA may have been associated with coexistent TFOA. However, little is known about how best to separate PFOA and TFOA symptoms. The criteria we used to define symptomatic PFOA were consistent with previous investigations[10]. No *a priori* sample size calculation was performed before the study started in 1990 as this study did not intend to compare two groups, but had a descriptive purpose. It is possible that analyses were underpowered to detect a significant difference in PFOA rates, however our study has one of the largest sample sizes with >15-year follow-up post-ACLR. Importantly, we included a number of AKP assessments (i.e., presence and persistence at both 1- and 2-years) and assessed its relationship with a number of PFOA assessments (i.e., symptomatic and radiographic OA at both 15- and 20-years) minimizing the chance of a type-II error. Although the criteria we used to define post-operative AKP have been used previously in a randomized controlled trial of graft type post-ACLR[7], the innumerable criteria used to define AKP in the general population and those post-ACLR reflect a lack of gold-standard diagnostic tool. Similar rates of AKP between our study

249 and others post-ACLR[4,15] support the external validity of our criteria. Finally, our results may
250 not be generalizable to the wider population without history of knee trauma/surgery.
251
252 In conclusion, the presence of AKP 1- and 2-years post-ACLR was not associated with
253 increased risk of radiographic or symptomatic PFOA at 15- or 20-years. Despite generally
254 larger risk ratios and wider confidence intervals, the persistence of AKP from 1- to 2-years
255 post-ACLR also did not increase the risk of longer-term PFOA. Although AKP is increasingly
256 recognized as more than a simple self-limiting disorder, PFOA does not appear to be a
257 sequelae of AKP post-ACLR.

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AUTHOR CONTRIBUTIONS

AGC, BEO, KMC and MAR conceived the project, BEO, IH and MAR recruited participants. AGC, BEO, IH and MAR collected clinical data, while RBG read all radiographs. AGC, BEO, IH, KMC and MAR contributed to data analysis and interpretation. All authors drafted or revised the manuscript for important intellectual content and approved of the final version of the paper. MAR managed the project, and obtained project funding. She takes full responsibility for the integrity of the work as a whole, from inception to finished article. E-mail address: m.a.risberg@nih.no

CONFLICT OF INTEREST STATEMENT

All other authors declare no conflict of interest.

ROLE OF THE FUNDING SOURCE

The funding bodies had no involvement in study design, interpretation of data, writing of the manuscript or the decision to submit the manuscript for publication.

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Table 1. Demographic characteristics and prevalence of anterior knee pain and patellofemoral osteoarthritis post-anterior cruciate ligament reconstruction (n=181 unless indicated otherwise)

	Number (%)
Age at surgery, years*	27 ± 8
Sex, female	76 (42)
Body mass index at 15-years, $kg.m^{-2}$*	26.5 ± 3.7
Isolated anterior cruciate ligament injury at 15-years	69 (38)
Anterior knee pain at 1-year#	36 (24)
Anterior knee pain at 2-years¶	33 (20)
Persistent anterior knee pain from 1- to 2-years¥	14 (10)
Radiographic patellofemoral osteoarthritis at 15-years	130 (72)
Radiographic patellofemoral osteoarthritis at 20-years§	115 (81)
Symptomatic patellofemoral osteoarthritis at 15-years	70 (39)
Symptomatic patellofemoral osteoarthritis at 20-years§	60 (42)

* mean ± standard deviation

28 participants with missing anterior knee pain data at 1-year (i.e., total n=153)

¶ 20 participants with missing anterior knee pain data at 2-years (i.e., total n=161)

¥ 38 participants with missing anterior knee pain data at 1- or 2-years (i.e., total n=143)

§ n=142 at 20-year follow-up

Table 2. The relationship between the presence and persistence of anterior knee pain and the presence of radiographic and symptomatic PFOA post-ACLR, adjusted for age, sex, body mass index and isolated vs. combined injury (risk ratios and 95% confidence intervals)

	15-years post-ACLR (n=181)		**20-years post-ACLR (n=142)**	
	Radiographic PFOA Yes/no (n=130/51)	Symptomatic PFOA Yes/no (n=70/111)	Radiographic PFOA Yes/no (n=115/27)	Symptomatic PFOA Yes/no (n=60/82)
Anterior knee pain 1-year post-ACLR				
Absent (referent) (n=117)	1.00	1.00	1.00	1.00
Present (n=36)	0.92 (0.60 to 1.42)	0.87 (0.50 to 1.59)	0.92 (0.58 to 1.46)	1.07 (0.57 to 1.98)
Anterior knee pain 2-years post-ACLR				
Absent (referent) (n=128)	1.00	1.00	1.00	1.00
Present (n=33)	0.98 (0.62 to 1.55)	1.47 (0.83 to 2.60)	0.93 (0.57 to 1.53)	0.70 (0.33 to 1.51)
Persistent anterior knee pain 1- to 2-years post-ACLR				
Absent (referent) (n=129)	1.00	1.00	1.00	1.00
Present (n=14)	1.12 (0.61 to 2.06)	1.41 (0.66 to 2.98)	1.03 (0.51 to 2.05)	1.21 (0.51 to 2.87)

ACLR, anterior cruciate ligament reconstruction; PFOA, patellofemoral osteoarthritis.