Osteoarthritis and Cartilage 23 (2015) 581–588

Osteoarthritis and Cartilage

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Meniscus treatment and age associated with narrower radiographic joint space width 2–3 years after ACL reconstruction: data from the MOON onsite cohort

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A R T I C L E I N F O

Article history:
Received 16 June 2014
Accepted 23 December 2014

Keywords:
Post-traumatic osteoarthritis
Knee
Radiographs
Joint space narrowing
ACL reconstruction
Meniscus

S U M M A R Y

Objective: To identify risk factors for radiographic signs of post-traumatic osteoarthritis (OA) 2–3 years after anterior cruciate ligament (ACL) reconstruction through multivariable analysis of minimum joint space width (mJSW) differences in a specially designed nested cohort.

Methods: A nested cohort within the Multicenter Orthopaedic Outcomes Network (MOON) cohort included 262 patients (148 females, average age 20) injured in sport who underwent ACL reconstruction in a previously uninjured knee, were 35 or younger, and did not have ACL revision or contralateral knee surgery. mJSW on semi-flexed radiographs was measured in the medial compartment using a validated computerized method. A multivariable generalized linear model was constructed to assess mJSW difference between the ACL reconstructed and contralateral control knees while adjusting for potential confounding factors.

Results: Unexpectedly, we found the mean mJSW was 0.35 mm wider in ACL reconstructed than in control knees (5.06 mm (95% CI 4.96–5.15 mm) vs 4.71 mm (95% CI 4.62–4.80 mm), $P < 0.001$). However, ACL reconstructed knees with meniscectomy had narrower mJSW compared to contralateral normal knees by 0.64 mm (95% C.I. 0.38–0.90 mm) ($P < 0.001$). Age ($P < 0.001$) and meniscus repair ($P = 0.001$) were also significantly associated with mJSW difference.

Conclusion: Semi-flexed radiographs can detect differences in mJSW between ACL reconstructed and contralateral normal knees 2–3 years following ACL reconstruction, and the unexpected wider mJSW in ACL reconstructed knees may represent the earliest manifestation of post-traumatic osteoarthritis and warrants further study.

Anterior cruciate ligament (ACL) reconstruction can effectively restore functional anteroposterior knee stability with a high rate of return to athletic activity, but individuals still have a risk of developing post-traumatic osteoarthritis (OA). Up to 50 percent of patients with an ACL tear with or without ACL reconstruction will develop radiographic signs of OA 10–20 years after injury[1,2]. A systematic review of radiographic OA in 596 subjects a minimum of 10 years after operative or non-operative treatment of ACL injury concluded that OA was present in both operative and non-operative

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http://dx.doi.org/10.1016/j.joca.2014.12.018
1063-4584/

groups[3]. Another systematic review of 31 studies with a total of 3069 subjects and a minimum of 10 years follow-up after ACL reconstruction reported that rates of radiographic OA ranged from 0 to 13 percent in subjects with isolated ACL injury, and 21–48 percent in subjects with concomitant meniscus injury[1]. The authors noted poor methodology scores in many of the papers with no standardization of treatment, rehabilitation or radiographs. They concluded that future studies should be prospective with clear inclusion/exclusion criteria, use a validated measurement system, report the rehabilitation protocol, and use regression to account for risk factors for development of OA[1].

A nested cohort was designed within the larger Multicenter Orthopaedic Outcomes Network (MOON) prospective longitudinal ACL reconstruction cohort to evaluate the initiation, progression, and risk factors for post-traumatic OA[4]. The unique features of this nested cohort include the younger age of patients ($\leq$35 years old at follow-up), no prior surgical treatment to either knee prior to enrollment, injured in sport, and no known ACL graft rupture or contralateral knee surgery during follow-up. The demographics, injury mechanism, meniscus and articular cartilage status, and surgical technique were all documented at enrollment, and the ACL rehabilitation guidelines were standardized[5–8]. The onsite follow-up included standardized posteroanterior metatarsophalangeal (MTP) radiographic views of both knees[9]. Semi-flexed MTP views have been validated and used to measure joint space width in multiple studies of ACL reconstruction and osteoarthritis incidence and progression[9–13].

The aim of the study was twofold: first, to determine whether MTP radiographs can detect joint space width differences between ACL reconstructed and contralateral control knees at an early time point after ACL reconstruction (2–3.3 years); and second, to identify risk factors for early radiographic signs of post-traumatic OA through multivariable analysis of joint space width differences. We hypothesized that the joint space width would be less in the ACL reconstructed knee than in the control knee, and that greater joint space width differences would be present in subjects who underwent arthroscopic partial meniscectomy than in those who had meniscus repair or no meniscal treatment.

Materials and methods

Subjects

Subjects were recruited from the MOON prospective cohort of subjects who underwent ACL reconstruction in the years 2005–2010. The study procedures followed were approved by the Institutional Review Boards of the coordinating center and each participating center, and each subject gave informed consent to participate in the research. These subjects completed a survey at the time of surgery containing questions addressing demographic information as well as validated outcome instruments including the Marx Activity Rating Scale[14]. At the same time, the surgeons also completed a standardized data collection form regarding the findings at surgery and details of treatment. Subjects were eligible for inclusion into the nested cohort imaging study if they were enrolled by one of four participating senior surgeons (JTA, CCK, RDP, or KPS) were 35 years or younger at the time of follow-up, had been injured while participating in a sport, had primary ACL reconstruction without concomitant MCL, LCL or PCL surgery, were at least 2 years and not more than 3 years 3 months post-surgery without revision ACL reconstruction during the follow-up period, and had never had surgery on the contralateral knee. Cases were excluded after participation if image quality problems on either knee were discovered upon analysis, including over-exposed images, under-exposed images, or markers that were not visible. Subjects were categorized by graft status (patellar tendon autograft, hamstrings tendon autograft, or allograft). One person with a hybrid allograft-autograft was categorized as allograft. Subjects were also categorized based on medial meniscus treatment including no tear, untreated tear, partial meniscectomy, or repair. Three people who had small excisions and large medial meniscal repairs were put into the meniscal repair category. Meniscal abrasion and trephination were collapsed into 'no treatment for tear'. Subjects were also categorized by articular cartilage status on the medial femoral condyle (normal/grade 1; grades 2/3/4). Radiographic measurements were obtained in 262 patients. (Fig. 1).

Radiographic technique

Subjects were positioned with their feet in 15° external rotation with the first metatarsophalangeal joint positioned directly underneath the front of the detector[9]. Their knees were bent until the patella touched the detector. Each knee was imaged individually with the beam focused at the center of the knee and a focal-film distance of 1.02 m (40 inches). Examination technique (settings on the X-ray machine) was varied to achieve optimal image quality. A free-standing standard containing balls of 5 mm diameter and 1 cm apart (Radiation Product Design, Inc, Albertville, MN) was placed next to the knee, vertical to the ground, at the fibular head to allow calibration for differences in magnification. Images were taken on a variety of instruments including: Siemens Polyphos (Siemens, Tarrytown, NY) and Shimadzu RADspeed machines (Shimadzu, Nakagyo-ku, Kyoto, Japan) using AGFA CR cassettes (Agfa HealthCare, Greenville, SC) as well as GE Definium (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) and Hologic DR (Hologic, Bedford, MA) digital machines. Each X-ray technologist was trained in subject positioning by the coordinating site study coordinator prior to beginning the study. Positioning consistency was maintained using identical positioning equipment across sites, including pads to insure proper foot rotation and calipers to position a rod directly beneath the detector front to guide positioning at the toes.

Image processing and radiographic joint space width measurement

Images were sent to the coordinating center in standard DICOM (Digital Imaging and Communications in Medicine) format, and multiple steps were employed to de-identify images and prepare them for analysis. XnView open-source image processing software (XnSoft, La Neuvilette, Reims, France) was used to convert images to TIFF format to erase all metadata and de-identify the images prior to analysis. Images were converted back to DICOM format using Adobe Photoshop CS6 (Adobe Systems Incorporated, San Jose, CA). OsiriX open source DICOM viewer software (www.osirix-viewer.com) was used to convert compressed DICOM images to uncompressed DICOM images for analysis.

Radiographic joint space width was measured using a previously described semi-automated computerized method that delineates the femoral and tibial margins of the joint and determines measurements of the medial compartment minimum joint space width (mJSW) as well as the joint space width at a fixed location 25% of the distance from the medial edge to the lateral edge of the tibia ($JSW_{0.25}$). The location-specific $JSW_{0.25}$ showed the most responsiveness in detecting longitudinal change in the Osteoarthritis Iniative (OAI) cohort[11]. Two individuals were removed from analysis only at the fixed location due to not having a valid measure at this point. Use of this measurement technique allows radiographic joint space width to be measured with a responsiveness for determining OA progression that is similar to MRI[11,15,16]. Images were evaluated with the reader viewing the left and right knee

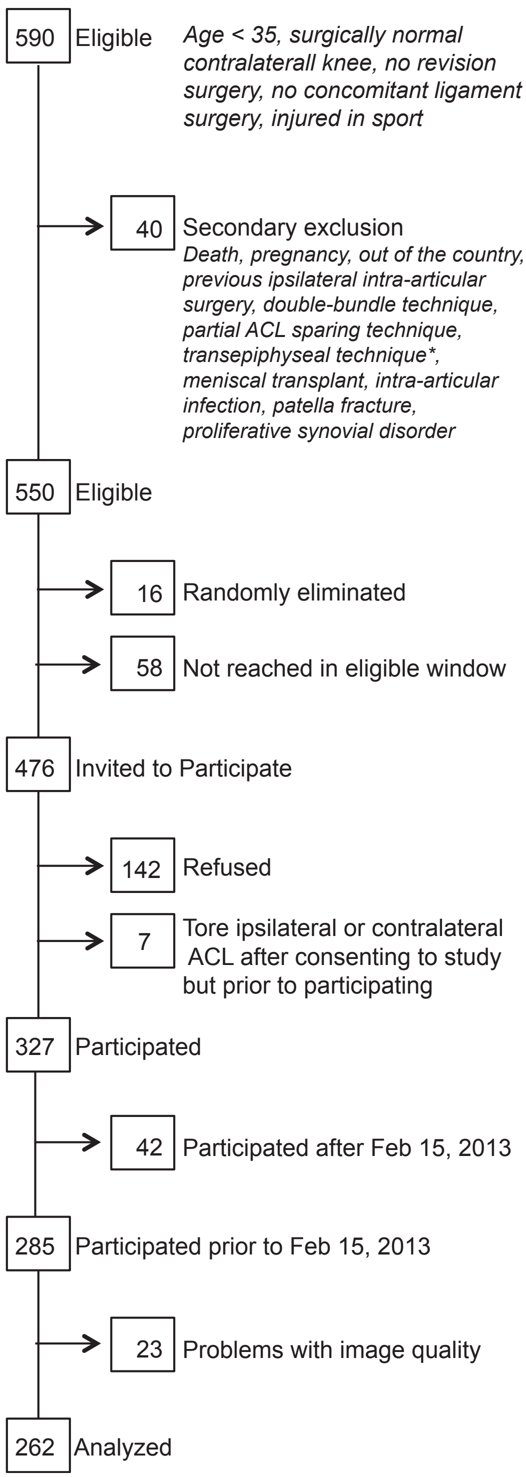

Fig. 1. Flow diagram showing the selection of study population, including all eligible and enrolled patients.

simultaneously. The reader was blind to patient demographic characteristics and chondral and meniscal status.

Statistical analysis

The outcome variable we assessed for this study was the joint space difference (JSD), which is the difference between the mJSW in the medial compartment of the ACL reconstructed knee compared to the mJSW in the medial compartment of the contralateral knee. A positive JSD indicates that the ACL reconstructed knee has a narrower joint space than the contralateral knee, while a negative JSD indicates that the ACL reconstructed knee has a wider joint space than the contralateral knee. A paired *t*-test was used to test significance for the difference in mJSW between ACL reconstructed and contralateral knees. Multivariable generalized linear models were constructed to assess multiple simultaneous variables including age, body mass index (BMI), baseline Marx activity level, graft source, medial meniscus treatment, and medial femoral articular cartilage status. We chose these variables because they demonstrated a strong association with patient reported outcomes at 6 and 10 years post-surgery in the MOON cohort from which our nested cohort was drawn[17]. Model assumptions of normality and heteroscedasticity were evaluated by examining Q–Q plots, estimating the optimal power parameter of a Box–Cox transformation, and performing Levene's test. For categorical variables with statistically significant coefficients for multiple categories, the model was run an additional time after changing the reference category for that variable to determine whether there was a statistically significant difference between those categories with different coefficients. A *P*-value of 0.05 was considered statistically significant; the Holm–Bonferroni method was used when comparing the different treatments to account for multiple comparisons since the model was run an additional time. A model was then constructed using the same methodology with $JSW_{0.25}$ as the outcome variable.

Results

Subjects

At 2 year follow-up, 590 subjects were eligible for inclusion in the nested cohort and 327 patients were evaluated on-site with semi-flexed MTP radiographs and patient-reported outcome questionnaires. Inclusions, exclusions and dropouts are presented in the patient flow diagram (Fig. 1). Measurements of bilateral mJSW were obtained in 262 of the 270 patients.

Descriptive data

The average age of the included subjects was 20 years at the time of surgery (range 12–33 years). There were 114 males and 148 females. Descriptive data including meniscus treatment and articular cartilage status are presented in Table I.

Joint space width

The mean medial compartment mJSW was 5.06 mm (95% CI 4.96–5.15 mm) for ACL reconstructed knees and 4.71 mm (95% CI 4.62–4.80 mm) for contralateral control knees, representing a medial JSD of −0.35 mm (95% C.I. −0.27 − −0.43 mm), ($P < 0.001$) (negative JSD indicates that ACL reconstructed knee has wider medial compartment mJSW than contralateral knee). 194 subjects (74%) had a negative JSD.

A multivariable generalized linear model to predict JSD was constructed which adjusted for age, gender, BMI, and baseline Marx activity level. Variables associated with larger JSD that were statistically significant included increased age ($P < 0.001$), meniscus repair ($P = 0.001$), and meniscectomy ($P < 0.001$). In terms of meniscus treatment, the coefficient for meniscectomy was largest, indicating the greatest JSD (See Table II). When the model was adjusted to make meniscectomy the reference group, the meniscus repair variable remained significant ($P < 0.02$), indicating that subjects with meniscectomy had significantly larger JSD than subjects with meniscus repair (See Table III). Graft type ($P = 0.17$

Table I
Baseline characteristics of the nested cohort. Categorical variables are expressed as percentages with *n* in parentheses. Continuous variables are shown as lower quartile/median/upper quartile

	Female (N = 148)	Male (N = 114)	Combined (N = 262)
Knee			
Left	47% (69)	54% (62)	50% (131)
Right	53% (79)	46% (52)	50% (131)
Age (years)	16.0/17.5/21.1	17.6/19.7/25.7	16.6/18.2/22.9
BMI (kg/m^2)	20.3/22.0/24.1	22.4/25.0/27.2	21.0/23.1/25.3
Marx activity at baseline (0–16)	12/16/16	11/15/16	12/16/16
Smoking Status			
Non smoker	95% (140)	88% (100)	92% (240)
Quit	3% (5)	10% (11)	6% (16)
Smoker	1% (2)	3% (3)	2% (5)
Unreported	1% (1)	0% (0)	0% (1)
Years of education completed	10.0/11.0/14.0	11.0/13.0/15.8	10.0/12.0/15.0
Graft			
Bone-Tendon-Bone autograft	61% (90)	62% (71)	61% (161)
Hamstring autograft	34% (51)	36% (41)	35% (92)
Allograft	5% (7)	2% (2)	3% (9)
Medial Meniscus treatment			
No tear	65% (96)	55% (63)	61% (159)
No treatment for tear	11% (16)	11% (12)	11% (28)
Repair	18% (26)	23% (26)	20% (52)
Excision	7% (10)	11% (13)	9% (23)
Medial Femoral Condyle chondral defect			
Normal/grade I	91% (135)	92% (105)	92% (240)
Grade II/III/IV	9% (13)	8% (9)	8% (22)

Table II
Regression coefficients for minimum joint space difference (mJSD) model. Positive values indicate the ACL reconstructed knee has narrower joint space than the contralateral control knee

Predictor	Coefficient	*(95% CI)*	*P* value
Intercept	−1.17	*(−1.82, −0.51)*	<0.001
Age (years)	0.042	*(0.025, 0.058)*	<0.001
Meniscus treatment			<0.001
Untreated meniscus tear	0.019	*(−0.21, 0.25)*	0.87
Meniscus repair	0.31	*(0.12, 0.49)*	0.001
Meniscectomy	0.64	*(0.38, 0.90)*	<0.001
Chondral lesion grade II,III,IV	−0.0024	*(−0.26, 0.26)*	0.99
Graft type			0.15
Hamstring graft	0.11	*(−0.045, 0.26)*	0.17
Allograft	−0.23	*(−0.62, 0.16)*	0.25
Female sex	−0.08	*(−0.23, 0.073)*	0.31
Baseline Marx activity (0–16)	−0.0032	*(−0.021, 0.014)*	0.72
BMI (kg/m^2)	−0.0035	*(−0.025, 0.018)*	0.75

Table III
Pairwise comparisons by meniscal status, including Holm–Bonferroni adjusted *P*-values

Pairwise comparison	Coefficient	*(95% CI)*	*P* value	Adjusted *P* value
Repair vs meniscectomy	−1.17	*(−0.63, −0.05)*	0.023	0.046
Untreated tear vs meniscectomy	−0.62	*(−0.95, −0.30)*	<0.001	0.013
Normal meniscus vs meniscectomy	−0.64	*(−0.90, −0.38)*	<0.001	0.008
Untreated tear vs normal meniscus	0.019	*(−0.21, 0.25)*	0.87	0.87
Meniscus repair vs normal meniscus	0.31	*(0.12, 0.49)*	0.001	0.017

hamstring, $P = 0.25$ allograft), chondral defect of the medial femoral condyle ($P = 0.99$), sex ($P = 0.31$), BMI ($P = 0.75$), and Marx activity ($P = 0.72$) were not significant contributors. (Fig. 2).

The same model was then constructed using $JSW_{0.25}$. In this analysis, age ($P < 0.001$) and meniscectomy ($P = 0.01$) remained significant contributors to JSD, but meniscus repair ($P = 0.42$) was no longer significant. (Table IV).

To demonstrate the relative differences in joint space width for two representative subjects, Fig. 3(A) shows a pair of knees with the ACL reconstruction side having a mJSW 1.97 mm wider than the contralateral side. Figure 3(B) shows a pair of knees with the ACL reconstruction side having a mJSW 1.24 mm narrower than the contralateral side.

Discussion

This study of 262 subjects 35 or younger at the time of follow-up who had no prior injury to either knee and bilateral fixed-flexion radiographs an average of 2.9 years after surgery demonstrated that the mJSW was 0.35 mm wider in the ACL reconstructed knee compared to the contralateral control knee, and that knees with medial meniscectomy or repair had mJSW that was relatively narrower compared to knees with untreated medial meniscus tears or normal medial menisci. JSD increased with increasing age, but there were no significant differences based on articular cartilage status, gender, BMI or activity level.

We selected this group of relatively young subjects to be able to measure the effects of injury and treatment on the development of early post-traumatic OA without concern for pre-existing osteoarthritis in either knee. This study represents the earliest prospective cohort of ACL reconstruction patients to show detectable differences in quantitative measures of joint space changes on plain radiographs.

Our study compared ACL reconstructed to contralateral control knees using a cross-sectional design at a single follow-up. We were surprised that the medial compartment mJSW was larger in the ACL reconstructed knees than in the contralateral control knees. A case control study by Tourville *et al.* of 39 ACL injured patients with presurgical and mean 46 month follow-up radiographs demonstrated a similar greater mJSW in the medial compartment of the ACL reconstructed knee compared to the contralateral control knee in three patients (7.7%) at follow-up[13]. Interestingly, three different subjects also had greater mJSW on the ACL-injured side at presurgery baseline, indicating that this change may occur early. Based on these findings, the authors recommended that cross-sectional evaluation of bilateral knees may be superior to use of the injured knee at baseline because of the changes that occur in the early post-injury period[13]. In addition, the authors measured the medial compartment mJSW in 32 control patients and found the side-to-side difference was 0.01 mm (95% C.I. −0.81–0.83 mm). Frobell noted an increase in cartilage volume of the central portion of the medial femoral condyle in 61 subjects from the Knee ACL nonoperative versus operative treatment (KANON) study who had ACL injury followed by early reconstruction, delayed reconstruction, or physical therapy. This finding was more pronounced in younger vs older subjects[18]. This age-related increase in cartilage volume may help to explain why our younger subjects had greater mJSW in their ACL reconstructed knees than our older patients. Another study demonstrated increased medial compartment cartilage volume in women 40 years of age or older with Kellgren Lawrence grade 2 osteoarthritis compared to healthy controls[19]. Multiple studies in dogs have shown a hypertrophic cartilage response after ACL transection which is present for up to 2 years and which differs from the changes seen in spontaneous, slowly developing OA[20–24]. Therefore, it remains unclear whether this

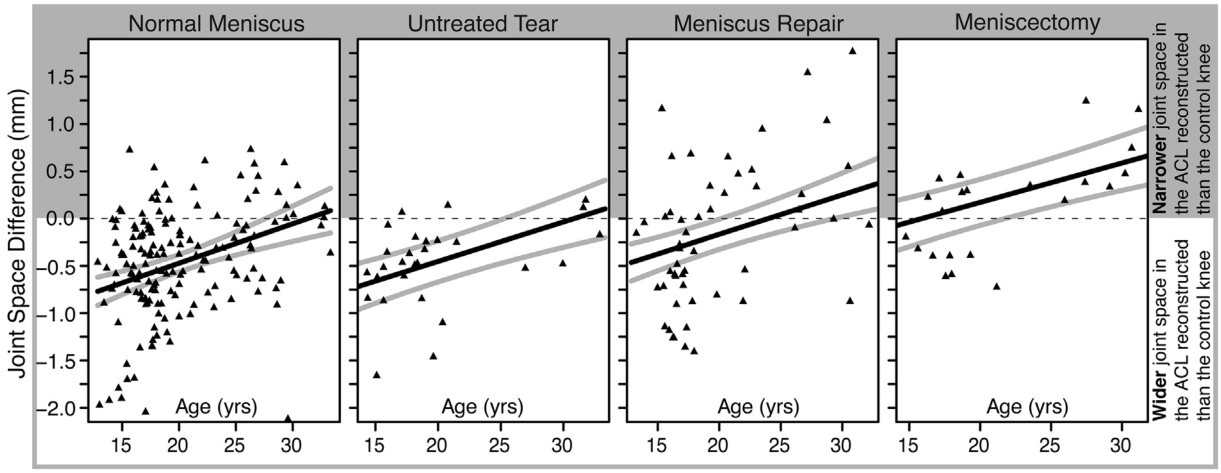

Fig. 2. Triangles represent raw data points, age plotted against JSD in each meniscal treatment group. Data is not adjusted for other variables. Black line is the predicted effect of age and meniscal treatment on JSD adjusted for sex, graft, BMI, and cartilage treatment. The surrounding gray lines represent the 95% confidence interval for the predicted effect. A dotted line is plotted at 0 on all graphs as a visual aid. One data point, from an 18 year old who had a meniscectomy and a JSD of 2.8 mm, is not presented.

increase in joint space width represents the earliest stage of post-traumatic OA, or an adaptive change in the cartilage biology that may prevent the progression of post-traumatic OA.

While Frobell[18] was able to detect changes on MRI as early as 12 and 24 months post-surgery, our study is the first to demonstrate that these changes can be detected with plain radiographs as early as 2–3 years post-surgery. This is important to provide a window of opportunity to potentially intervene in the earliest stages of post-traumatic OA. As we expected, subjects with partial medial meniscectomy demonstrated the greatest JSD. A systematic review of 31 studies with a minimum of 10 years follow-up reported that rates of radiographic OA ranged from 0 to 13 percent in subjects with isolated ACL injury, and 21–48 percent in subjects with concomitant meniscus injury[1]. A subsequent study of 221 subjects with radiographic follow-up at 10–15 years postoperatively reported radiographic OA in 62 percent of subjects with isolated ACL injury and 80 percent of patients with a concomitant meniscus tear[25]. Another systematic review of 16 studies with minimum 10 year radiographic follow-up that included a meta analysis of 1554 ACL reconstructions reported an OA incidence of 16 percent in isolated ACL injury and 50 percent in knees with associated meniscus tears[2].

Table IV
Regression coefficients for fixed location $JSD_{0.25}$ model. Positive values indicate the ACL reconstructed knee has narrower joint space than the contralateral control knee

Predictor	Coefficient	*(95% CI)*	*P* value
Intercept	−1.14	*(−1.74, −0.55)*	<0.001
Age (years)	0.031	*(0.017, 0.046)*	<0.001
Meniscus treatment			0.017
Untreated meniscus tear	−0.17	*(−0.38, 0.041)*	0.12
Meniscus repair	0.069	*(−0.098, 0.24)*	0.42
Meniscectomy	0.30	*(0.065, 0.53)*	0.013
Chondral lesion grade II,III,IV	−0.076	*(−0.31, 0.16)*	0.53
Graft type			0.30
Hamstring graft	0.039	*(−0.10, 0.18)*	0.58
Allograft	−0.24	*(−0.60, 0.11)*	0.18
Female sex	0.018	*(−0.12, 0.16)*	0.80
Baseline Marx activity (0–16)	−0.0099	*(−0.026, 0.0057)*	0.22
BMI (kg/m^2)	0.0051	*(−0.014, 0.025)*	0.61

In a study of 19 ACL injured subjects treated without surgery at mean follow-up of 34.3 months post-injury, there were no subjects with decreased radiographic joint space width. However, in contrast to our subjects, none of the subjects in this study had associated meniscus or articular cartilage injury[26].

We were also surprised to see that subjects with medial meniscus repair had a narrower mJSW on the ACL reconstructed knee compared to the contralateral knee when compared to untreated meniscus tears or normal menisci. This finding is supported by two clinical outcome studies on ACL reconstruction. First, Barenius *et al.,* in data from the Swedish National ACL Registry, found medial meniscus repair to be predictive of worse patient reported outcomes (defined as treatment failure) at 2 years postoperatively[27]. Second, in a separate ACL reconstruction population within the MOON cohort, medial meniscus repair predicted worse patient reported outcomes at 6 years postoperatively[17]. Furthermore, a recent systematic review which assessed the healing rate of meniscus repairs with and without ACL reconstruction at a minimum of 5 years follow-up showed that the failure rate ranged from 20.2 to 24.3 percent, and there was no significant difference between the repairs with or without concomitant ACL reconstruction[28]. It is likely that a number of the subjects in our study who had medial meniscus repair experienced failed repair and subsequent meniscal degeneration or further tearing and loss of function, which contributes to a difference in JSD as compared to those with normal menisci.

While a previous study showed that mJSW was a less sensitive measure than location-specific joint space width for detecting the radiographic progression of idiopathic OA, mJSW was the more sensitive measure in our population[11]. This may be related to differences in the pathogenesis of post-traumatic OA compared to idiopathic OA, or may be due to differences in comparing contralateral knees to one another on a cross sectional basis vs comparing the same knees over time.

A limitation of our study is availability of radiographs at only a single time point postoperatively. Given the wider joint space in the ACL reconstructed knees compared to the contralateral knees in our

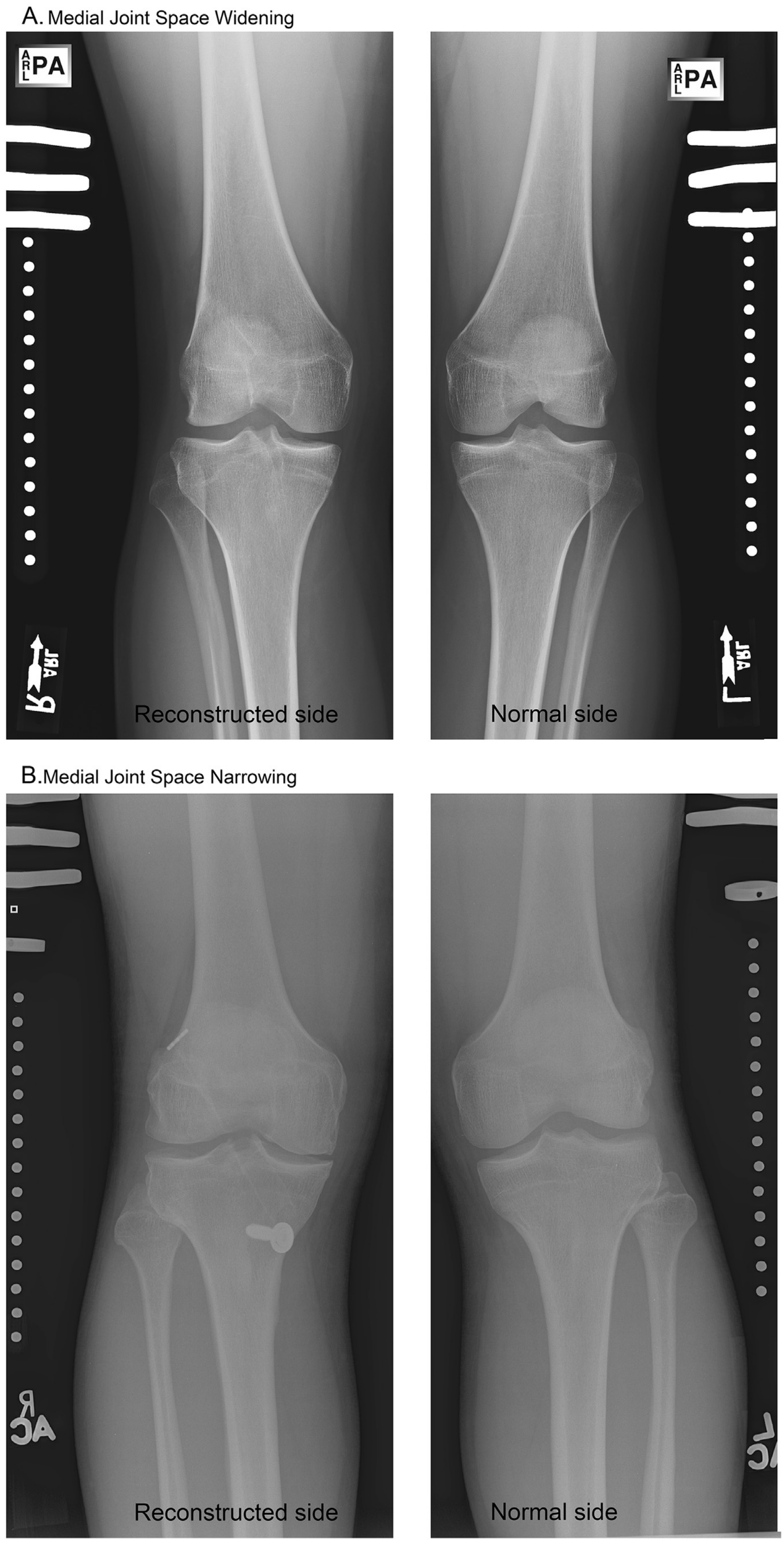

Fig. 3. Representative images. A shows images from a 13 year old female patient who had a normal medial meniscus and a medial compartment mJSW 1.97 mm wider on the ACL reconstructed side compared to the contralateral control side. B shows images from a 27 year old male patient who had a partial medial meniscectomy and a medial compartment mJSW 1.24 mm narrower on the ACL reconstructed side compared to the contralateral control side.

subjects and reports of early post-injury widening occurring in other series, the availability of baseline MTP radiographs would have been useful and would have provided the ability to measure progression of mJSW differences. In addition, even though meniscus repair and meniscectomy were associated with narrower mJSW, many subjects with these treatments still had no significant difference in mJSW between the ACL reconstructed knee and the contralateral normal knee. Follow-up visits with repeated MTP radiographs will determine whether JSD increases in the meniscus repair and meniscectomy subjects in the future.

In conclusion, our study shows a wider medial compartment mJSW in ACL reconstructed knees compared to contralateral control knees at 2–3 year follow-up, an unexpected finding that warrants further study. In addition, our multivariable model showed that as compared to reconstructed knees with normal menisci, those that had meniscectomy or meniscus repair were associated with relatively narrower JSW on the ACL reconstructed knee compared to the control knee, but meniscectomy had the larger effect. This indicates that while knees with repaired meniscus tears do not show results as extreme as those with meniscectomy, a repair does not restore the state of the knee to that of one with a normal meniscus. This finding supports investigation into possible improvements, particularly if our data predicts long term osteoarthritis development. Finally, JSD difference increased with increasing age. To our knowledge, this is the first study to detect differences in joint space width between ACL reconstructed and contralateral control knees using plain radiographs 2–3 years after surgery in a group of younger patients without prior knee injury who were injured in sport. Our findings support the notion that structural features of osteoarthritis can be identified at early time points after surgery using plain radiographs.

Declaration of authorship

Concept and design: JTA, CLD, WRD, BCF, DCF, LJH, MHJ, CCK, HLO, RDP, EKR, KPS, CSW. Collection and assembly of data: JTA, CLD, JD, LJH, CCK, RDP, EKR, EAS, KPS. Analysis and interpretation of data: JD, BCF, MHJ, NAO, HLO, EKR, KPS, CSW. Statistical Expertise: MHJ, NAO, EKR. Drafting of the article: MHJ, EKR. Obtaining funding: KPS. Provision of study patients: JTA, CCK, RDP, KPS. Technical and administrative support: CLD, JD, LJH, EAS. All authors participated in revising of the article critically for important intellectual content and final approval of the version to be submitted.

Morgan H. Jones (jonesm7@ccf.org), Kurt P. Spindler (spindlk@ccf.org), and Emily K. Reinke (emily.reinke@vanderbilt.edu) take responsibility for the integrity of this work as a whole from inception to completion.

Funding source

This study was funded by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases, grant numbers 5R01 AR053684 (to K.P.S.) and 5 K23 AR052392-04 (to W.R.D.). Dr Spindler has received unrestricted educational funds from Smith & Nephew and unrestricted research funds from DonJoy. This work was also supported by CTSA award No. **UL1TR000445** from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. No funding source had involvement in study design, collection, analysis of data, writing of the manuscript, or decision to submit the manuscript for publication.

Competing interests

KPS serves on the scientific advisory board for Cytori, has received consultant fees from the National Football League and Service Excellence, and has received fees from a patent for intra-articular healing. DCF has received consultant fees from Smith and Nephew and Sanofi. The other authors have no conflicts of interest to disclose regarding this manuscript.

Acknowledgments

The authors acknowledge the work of radiology technologists from the Cleveland Clinic, Brendan FitzGerald RT(R), Lisa Hansinger RT(R), Jean Kovacic RT(R), Jennifer Mahony RT(R)(BD)CBDT, Katherine Malysa RT(R), Nathan Noblett RT(R), Austin Retherford RT(R), Diane Smith RT(R); from The Ohio State University Wexner Medical Center, Melissa DeSilva RT(R), Amy Hillyer RT(R), Jessica Malik BSRT(R)(CT), Allison Phelps RT(R)(CT), Terri Sisco RT(R), James Snipes BSRT(R)(CT)(MR), Tye Thompson RT(R)(CT)(MR), Sandy Taylor RT(R)(CT); and from Vanderbilt University Medical Center, Nehayet Abdulkader RT(R), Emily Cope RT(R), Marisa Hairston-Fisher RT(R), Christopher Herod RT(R), Aleta Lovison RT(R), Julie Payne RT(R).

The authors also acknowledge the work of contributors invaluable for this work: for assistance with data collection from the Cleveland Clinic, Lynn Borzi MBA RN CCRC, Maxine Cox, Michelle Hines RN, Pam Koeth PA-C, Valerie Walker–Lewis, Maya McCauley, Lisa Hegemier PA-C, Leah Schmitz MPAS PA-C; and The Ohio State University Wexner Medical Center, Angela D. Pedroza MPH, Breanna Beck PA-C ATC, Paul Montesanti CIP, Kari Stammen ATC; for assistance with data preparation, Suzet Galindo-Martinez MS, Zhouwen Liu MS, and Charles Dupont; for assistance with statistical concerns, Frank E Harrell, Jr. PhD and Samuel K Nwosu MS; for assistance with image de-identification and preparation for analysis, Baxter P Rogers PhD and Gian Franco Scaramuzza; and for data safety monitoring, Gene Hannah MD.

The authors thank MOON (Multicenter Orthopaedic Outcomes Network) members from the following institutions for their support and contributions: the Hospital for Special Surgery, the Ohio State University, the University of Colorado, the University of Iowa, Vanderbilt University, and Washington University in St. Louis.

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