Arthroscopic Articular Cartilage Scores of the Canine Stifle Joint with Naturally Occurring Cranial Cruciate Ligament Disease

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Abstract

Objective This study aimed to evaluate frequency, location and severity of cartilage pathology in dogs with naturally occurring cranial cruciate ligament (CCL) disease.

Study Design Stifle arthroscopic video recordings ($n = 120$) were reviewed. A modified Outerbridge classification system (MOCS) (0–4) was used to score cartilage at 10 locations in the femorotibial (medial and lateral femoral condyles and tibial plateaus) and patellofemoral compartments (proximal, middle and distal locations of the patella and femoral trochlear groove) of the stifle joint. Synovial pathology was scored and the presence of a medial meniscal tear was recorded. A Kruskal–Wallis test was used to evaluate association of location and synovitis with cartilage score; and presence of meniscal tear with cartilage and synovitis scores. Bonferroni correction was utilized and $p < 0.05$ was considered significant.

Results Cartilage pathology and synovitis were identified in all joints. Overall cartilage severity scores were low (median MOCS 1). The median MOCS of the proximal trochlear groove (2) was significantly higher than all other locations evaluated. Higher synovitis scores were significantly associated with higher cartilage severity scores and a medial meniscal tear had no association with cartilage severity scores or synovitis.

Conclusion Arthroscopic articular cartilage lesions are common in dogs with CCL disease at the time of surgical intervention, although the severity of cartilage damage is mild. The proximal trochlear groove of the femur had the most severe cartilage score in the stifle joint.

Keywords

- canine
- arthroscopy
- stifle
- osteoarthritis
- cartilage

Introduction

Cranial cruciate ligament disease is a common musculoskeletal disorder in the dog and is the leading cause of osteoarthritis in the canine stifle joint.^{1–3} Osteoarthritis is characterized by chronic, progressive deterioration of all

joint components, leading to pain and functional disabilities in dogs and human beings.^{1,4} Despite surgical intervention for the management of cranial cruciate ligament disease, osteoarthritis progresses over time in the canine stifle, as well as in the human knee post-anterior cruciate ligament repair.^{5–8}

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The current literature on the presence and severity of stifle osteoarthritis in dogs with cranial cruciate ligament disease mainly focuses on the use of radiographic evaluation^{5,9} however, a few reports describe arthroscopic inspection of the cartilage and the severity of the pathological changes.^{6,10–12} In a retrospective study of dogs with cranial cruciate ligament deficient stifles, the median cartilage score in the medial portion of the femorotibial joint compartment, at the time of surgery, was 0, representing normal cartilage.¹¹ However, on second-look arthroscopic evaluation of dogs with complete cranial cruciate ligament tears treated with a tibial plateau levelling osteotomy, the articular cartilage in the femorotibial compartment had progressed to grade 3–4 modified Outerbridge cartilage classification system (MOCS) scores.⁶ These studies suggest that the articular cartilage is visibly normal at the time of surgery in the femorotibial compartment, yet despite surgical intervention, cartilage damage ensues. In addition to examination of the main weight bearing femorotibial portion of the stifle joint, the articular cartilage of the patellofemoral (PF) compartment has also been evaluated in dogs with cranial cruciate ligament disease.¹² Interestingly, a high frequency of dogs with cranial cruciate ligament disease had articular cartilage changes in the PF compartment at the time of surgical intervention.¹² This appears to be different from the medial femorotibial compartment where the cartilage was scored as normal at the time of surgical intervention.¹¹

In people, PF osteoarthritis pain is one of the most common sequelae following anterior cruciate ligament injury¹³ and patients with more severe PF osteoarthritis have worse final clinical outcomes.¹⁴ Long-term follow-up after anterior cruciate ligament injury and repair has shown progression of osteoarthritis occurring in both the femorotibial and the PF knee joint compartments.^{15,16} In a study evaluating articular cartilage in patient's post-anterior cruciate ligament repair, the majority of the cartilage lesions following surgery was located in the PF joint rather than the femorotibial joint.⁷ Another study has also shown similar trends of more significant osteoarthritis progression in the PF joint as compared with the femorotibial joint on second-look arthroscopy.¹⁷ In the dog, the description and comparison of cartilage changes in the stifle joint compartments, at the time surgical intervention and in long term follow-up, are limited.^{6,11,12} An understanding of early arthroscopic cartilage changes will be beneficial when evaluating long-term patterns of osteoarthritis progression with the various surgical techniques. Therefore, the aim of this study is to evaluate the articular cartilage in both the femorotibial and PF compartments in the canine stifle joint with cranial cruciate ligament disease at the time of surgery to determine initial cartilage health prior to intervention.

The main objectives of this study were to determine the frequency, location and severity of articular cartilage lesions in the canine stifle with naturally occurring cranial cruciate ligament disease. We also evaluated the relationship of synovitis and meniscal injury to the cartilage severity score. We hypothesized that the articular cartilage in the PF compartment will have higher cartilage severity scores as com-

pared with the femorotibial joint compartment. In addition, the authors hypothesized, based on subjective arthroscopic observation of numerous stifle joints, that the lateral tibial plateau cartilage surface will have higher scores than the medial tibial plateau. Lastly, we hypothesized higher synovitis scores would be correlated with more severe cartilage damage and the presence of a bucket handle medial meniscal tear would not be associated with the cartilage score.

Materials and Methods

Dogs having treatment for cranial cruciate ligament disease via arthroscopic stifle exploration and surgical stabilization at the University of Pennsylvania were included in this study. All owners consented to the procedure and use of data for study purposes. The dogs had no prior history of orthopaedic disease or surgery performed on the affected stifle and had clinical signs of cranial cruciate ligament disease in the affected limb, including lameness, stifle effusion and stifle pain. Age, breed, gender and weight were recorded. If cranial drawer and tibial thrust were not appreciated on physical examination, cranial cruciate ligament pathology was diagnosed at the time of arthroscopic exploration. Stifle instability was defined as the ability to palpate any amount of gross movement in the stifle via the cranial drawer and tibial thrust tests. Dogs with palpable instability were considered unstable, even if intact fibres were detected via arthroscopy, whereas a stable stifle had partial tearing of the cranial cruciate ligament identified via arthroscopy without any palpable instability.

A total of 120 high-definition video recordings of stifle explorations using a 3-chip camera and a 2.7 mm arthroscope (Stryker, Kalamazoo, Michigan, United States) were performed by a single board-certified surgeon (KAA) with > 10 years of experience in canine stifle arthroscopy at the University of Pennsylvania. Twelve of the dogs had bilateral cranial cruciate ligament tears and had an arthroscopic exploration and stabilization performed at different time points. Complete stifle explorations were required for inclusion and were defined as having videos of the PF joint, supratrochlear joint pouch, the medial or lateral trochlear joint space, the cranial and caudal cruciate ligaments, the medial and lateral femorotibial joints and the medial and lateral menisci.

All cartilage and synovial scoring was performed on the video recordings at a later time point (at least 1 year) from the time of surgery by one investigator (KAA). The articular cartilage evaluated included the central weight bearing surface of the medial and lateral femoral condyles, the cartilage exposed on the medial and lateral tibial plateau (central and axial to the medial and lateral menisci) and the proximal, middle and distal regions of the patella and the femoral trochlear groove (► **Fig. 1**). A MOCS was used to score these aforementioned regions^{18–20} (► **Table 1**) and a previously described synovial pathology scoring system was used to score the synovitis in the supratrochlear stifle joint pouch (► **Table 2**).²² In addition, the medial meniscus was arthroscopically inspected and the presence or absence of a caudal horn bucket handle medial meniscal tear was recorded.

Fig. 1 Locations of articular cartilage scoring within the canine stifle joint. In the patellofemoral joint compartment, 3 locations (proximal, middle and distal) were examined on the articular surface of both the trochlear groove of the femur (green) and under side of the patella (yellow). The medial and lateral femoral condyles (blue) and the tibial plateaus (red) locations were scored in the femorotibial joint compartment. TP, trochlear groove proximal; TM, trochlear groove middle; TD, trochlear groove distal; PP, patella proximal; PM, patella middle; PD, patella distal; FCM, femoral condyle medial; FCL, femoral condyle lateral; TPM, tibial plateau medial; and TPL, tibial plateau lateral.

Table 1 Modified Outerbridge classification system for arthroscopic scoring of articular cartilage^{21–23}

Gross characteristics	Score
Smooth surface	0
Slightly fibrillated/roughened surface	1
Fibrillated surface with focal partial thickness lesions	2
Deep lesions with surrounding damage	3
Large areas of severe damage	4

Other less significant pathology of the menisci was not recorded in this study.

Descriptive statistics were calculated. Categorical data are expressed as frequencies. To account for the non-normality of the data, continuous variables are expressed as median values and ranges. The Kruskal–Wallis test was used to evaluate the association of joint location and synovitis grade with cartilage score; and presence of a bucket handle tear with cartilage and synovitis score. Bonferroni correction for multiple comparisons was used and $p < 0.05$ considered significant.

Results

This study included 120 stifles (62 right, 58 left) from 108 dogs with cranial cruciate ligament disease. There was a total

Table 2 Synovial arthroscopic pathology scoring system²²

Gross characteristics		Score
Normal	Opal white, semi-translucent, smooth, with sparse well-defined blood vessels	0
Slight	Focal involvement, slight discoloration, visible proliferation/fibrillation/thickening, notable increase in vascularity	1
Mild	Diffuse involvement, slight discoloration, visible proliferation/thickening, moderate vascularity	2
Moderate	Diffuse involvement, severe discoloration, consistent notable proliferation/fibrillation/thickening, moderate vascularity	3
Marked	Diffuse involvement, slight discoloration, consistent and marked proliferation/fibrillation/thickening, diffuse hypervascularity	4
Severe	Diffuse involvement, slight discoloration, severe proliferation/fibrillation/thickening, thickening to the point of fibrosis, severe hypervascularity	5

of 114 neutered and 6 entire dogs, 68 were spayed females, 46 castrated males, 2 females, and 4 males. This population of dogs had 106 unstable and 14 stable stifles. The median age was 5 years (range: 1–12 years) and the median body weight was 36.8 kg (range: 6.4–81.8 kg). The breeds included mixed breed ($n = 36$), Labrador Retriever ($n = 16$), Newfoundland Mastiff ($n = 7$), Golden Retriever ($n = 7$), Rottweiler ($n = 5$), American Pit Bull Terrier ($n = 5$), Boxer ($n = 4$), German Shepherd Dog ($n = 4$), Bernese Mountain Dog ($n = 3$), Belgian Malinois ($n = 2$), Beagle ($n = 2$), English Mastiff ($n = 2$) and 1 of each of Bouvier Des Flanders, Doberman Pinscher, Weimaraner, English Bulldog, Cane Corso, Portuguese Water Dog, Spanish Water Dog, Whippet, Norwegian Elkhound, Alapaha Blue Blood Bulldog, Yorkshire Terrier, Great Pyrenees, Great Dane, Cairn Terrier and English Pointer. The breeds with bilateral disease included Newfoundland Mastiff ($n = 2$), Labrador Retriever ($n = 2$), mixed breed ($n = 3$) and one of each of the following breeds, Bernese Mountain Dog, Rottweiler, Boxer, Yorkshire Terrier and Cairn Terrier.

Cartilage lesions were identified in at least one location in all 120 stifles (► Fig. 2). The overall median MOCS score was 1 and the scores varied depending on location within the stifle joint ($p < 0.001$). The median MOCS score of the proximal, middle and distal patella; the middle and distal trochlear groove; and the medial and lateral femoral condyles and tibial plateaus was 1. The proximal trochlear groove had a median MOCS score of 2 (► Table 3). The proximal trochlear groove had significantly higher cartilage scores than all of the other sites examined ($p < 0.001$). The middle trochlear groove had significantly higher scores than the distal trochlear groove ($p < 0.001$), the proximal patella ($p < 0.001$) and the middle patella ($p < 0.001$). The distal patella has a significantly higher scores when compared with the

Fig. 2 Arthroscopic images of the canine stifle joint with cranial cruciate ligament disease. (A) Smooth articular cartilage of the medial femoral condyle assigned a modified Outerbridge score of 0. (B) The medial portion of the femorotibial compartment following a partial caudal horn medial meniscectomy due to a bucket handle meniscal tear. Articular cartilage of medial femoral condyle and the tibial plateau were given a modified Outerbridge score of 1 due to the roughened cartilage surface. (C) Articular surface of the lateral tibial plateau showing a fibrillated surface with partial thickness lesions that was assigned a score of 2. (D) The patellofemoral joint compartment identifying the cartilage surface of both the patella and the trochlear groove with deep lesions and surrounding damage, a modified Outerbridge score of 3 was assigned to both surfaces. (E) The supratrochlear joint pouch of the stifle joint showing diffuse changes, moderate hypervascularity and notable proliferation, fibrillation and thickening. A gross synovial pathology score of 3 was assigned.

Table 3 Distribution of the number of times a modified Outerbridge score (0–4) was assigned to a specific location in the stifle joint

MOCS score	Patellofemoral joint Compartment						Femorotibial joint compartment			
	Patella			Femoral trochlear groove			Femoral condyle		Tibial plateau	
	Proximal	Middle	Distal	Proximal	Middle	Distal	Medial	Lateral	Medial	Lateral
0	39	31	4	0	6	30	18	22	3	2
1	61	67	66	10	63	61	71	66	76	57
2	13	15	37	77	48	15	21	21	38	48
3	2	3	6	30	3	1	9	8	2	2
4	0	0	0	3	0	0	1	0	1	0
No score	5	4	7	0	0	13	0	3	0	11

Abbreviation: MOCS, modified Outerbridge classification system.

proximal and middle patella locations ($p < 0.001$) as well as the trochlear groove distal ($p < 0.001$). The lateral tibial plateau had significantly higher scores than the distal trochlear groove ($p < 0.001$) and the proximal and middle patella ($p < 0.001$), and the medial tibial plateau had significantly higher cartilage scores than the proximal patella ($p < 0.001$) (►Fig. 3).

A caudal horn, bucket handle medial meniscal tear was arthroscopically identified in 40 of the 120 stifles (33.3%) examined in this study. The presence of a bucket handle medial meniscal tear was not associated with an increased MOCS or synovitis scores.

All 120 stifles examined had synovitis and the median synovitis score in the supra trochlear joint was 3. Higher synovitis scores were associated with increased cartilage scores ($p < 0.001$). Stifles with a synovitis score of 3 had significantly higher cartilage scores than stifles with a score of 2 ($p < 0.001$). Stifle synovitis scores of 4 have significantly higher cartilage scores than stifles with a score of 2 ($p < 0.001$) and stifles with a score of 3 ($p < 0.002$).

Discussion

In this group of dogs with cranial cruciate ligament disease, articular cartilage lesions were commonly observed in the stifle joint and some degree of cartilage pathology was

identified in all 120 stifles examined. The severity of cartilage lesions varied depending on location, where the proximal trochlear groove had a significantly higher median MOCS score than all other locations evaluated in both the femorotibial and PF joints.

A combination of mechanical and biological pathways plays complex roles in the development of osteoarthritis^{21–23} however, it is well established that altered joint mechanics result in progressive articular cartilage damage.^{22,23} In *ex vivo* models of cranial cruciate ligament disease, using canine cadavers, the contact and alignment of the femorotibial and PF stifle joint compartments were altered following cranial cruciate ligament transection.^{24–26} In the femorotibial joint, an increase in peak pressure magnitude and a decrease in the contact area between femur and tibia were identified, as well as a shift of this contact area to a more caudal location.^{24,26} In addition, axial rotation (internal) of the tibia was significantly different from stifles with an intact cranial cruciate ligament.²⁴

These findings of altered mechanics in cadaveric femorotibial joints are consistent with the clinical findings from this study in that gross cartilage changes were observed in both the medial and lateral femorotibial joint compartments. The MOCS scores were low on all surfaces examined without any significant differences between sites examined in the femorotibial compartment. The median MOCS score was not

Fig. 3 Box and whisker plots of the modified Outerbridge cartilage scores in the canine stifle joint. The bold line within the box represents the median cartilage score (50th percentile) and the box represents the 25th and 75th percentiles. Whiskers above and below the box indicate the maximum and minimum data scores. '*' denotes the trochlear groove proximal site has a significantly higher modified Outerbridge score; '#' signifies the trochlear groove middle has a significantly higher modified Outerbridge score; '^' signifies the distal patella has a significantly higher modified Outerbridge score; '\$' denotes the lateral tibial plateau has a significantly higher modified Outerbridge score; and '@' indicates the medial tibial plateau has a significantly higher modified Outerbridge score. PP, patella proximal; PM, patella middle; PD, patella distal; TP, trochlear groove proximal; TM, trochlear groove middle; TD, trochlear groove distal; TPM, tibial plateau medial; FCM, femoral condyle medial; TPL, tibial plateau lateral; FCL, femoral condyle lateral.

significantly higher in the lateral tibial plateau location in comparison to the medial tibial plateau site (►Table 3, ►Fig. 3). We, therefore, rejected our hypothesis that the lateral tibial plateau would have significantly higher MOCS scores than the medial location. In addition, as expected and similar to a previous study, the presence of a bucket handle tear was not associated with more severe cartilage scores in the medial femorotibial joint compartment¹¹ or in any of the other sites examined. It has been suggested that the size of the meniscal tear, its dynamic position, and the frequency of displacement may affect its ability to cause clinically relevant cartilage damage.²⁷ These associations are beyond the scope of this study and further investigation into the types of meniscal tears and cartilage damage is warranted.

In comparison to this study, a previous retrospective case series examining the medial femorotibial joint of 290 canine stifles with cranial cruciate ligament disease, the median MOCS score, at the time of surgery, of both the femur and tibia was 0, indicating that the cartilage appeared visually normal.¹¹ This study only examined the medial femorotibial compartment, but differed from our results, as cartilage pathology was not commonly identified.¹¹ The reason for this difference is not known. A limitation and a possible reason for this discrepancy between studies is observer variability of the MOCS.²⁰ DeWeese and colleagues examined the variability of the MOCS in canine cartilage and found the

inter- and intra-observer agreement to be fair and substantial respectively.²⁰ Agreement in scoring improved when the same observer with experience in arthroscopy scored the cartilage.²⁰ In addition, there was better agreement at the ends of the MOCS as compared with the middle scores.²⁰ In our study, we attempted to decrease variability based on these results, by utilizing the same experienced observer to score all of the cartilage surfaces.

In the PF joint, there was a significant, progressive decrease in cartilage severity scores from proximal to distal in the trochlear groove. In addition, the distal articular surface of the patella had significantly greater cartilage scores than the proximal and middle locations on the patella. This same pattern of articular cartilage damage in the PF joint was previously reported in 40 canine stifles.¹² This pattern of cartilage lesions appears to correspond to the altered mechanics reported in the PF joint compartment with cranial cruciate ligament transection; however, the exact mechanical change causing the cartilage damage is uncertain.^{25,28} In an *ex vivo* cadaveric study, although the overall retropatellar force is decreased across the entire PF joint with cranial cruciate ligament transection, the peak pressure location moved more proximally in the trochlear groove and alignment of the patella was altered resulting in an increased patellar tilt.²⁵ In that cadaveric study, where the femorotibial flexion angle was kept constant, this proximal shift in contact area was suggested to be the reason for the increased

cartilage damage at the proximal trochlear groove location.^{12,25} Conversely, in an *in vivo* evaluation of PF joint kinematics using single, sagittal plane fluoroscopy in dogs with cranial cruciate ligament deficient stifles, the entire patella was displaced distally throughout the gait cycle.^{28,29} This distal displacement of the patella was attributed to the increased femorotibial flexion angle noted in dogs with cranial cruciate ligament deficient stifles at a walk and suggested that the proximal trochlear groove cartilage lesions may be induced by inadequate PF contact²⁸ rather than a proximal shift in contact area.^{12,25} Despite the unknown reason for induction of cartilage damage at the proximal trochlear groove location, it is known that abnormal joint loading and alignment are risk factors for the development of osteoarthritis.^{22,23}

In this group of dogs studied, the proximal trochlear groove location in the PF compartment had the greatest cartilage severity score in the stifle joint, even when compared with the main weight bearing femorotibial joint compartment. The significance of the PF compartment having the highest median MOCS score in this early time period following a cranial cruciate ligament diagnosis is not known, although it suggests that the mechanical alterations may be most significant at this location. Interestingly, in people, the PF joint is a common source of pain and functional limitations following anterior cruciate ligament injury.^{13,14,30,31} In one study, radiographic PF osteoarthritis with associated clinical symptoms was reported in ~50% of people following anterior cruciate ligament injury and repair.³² The presence of PF osteoarthritis in people is not a trivial outcome following anterior cruciate ligament repair, as patients with PF osteoarthritis present with more knee complaints and functional disabilities that result in worse clinical outcomes.^{14,31,32} In addition, reports suggest that osteoarthritis may progress more quickly in the PF joint rather than the femorotibial joint in patients.^{19,20} Progression of the osteoarthritis in the PF joint may indicate that the mechanical alterations are not restored with anterior cruciate ligament repair and disease in the PF joint can lead to clinical symptoms. Osteoarthritis severity may also differ depending on the type of surgical repair^{7,33} and further investigation into the mechanics of the PF joint following anterior cruciate ligament repair is warranted. Clinical evaluation of the PF joint in dogs with cranial cruciate ligament disease is limited. Radiographic identification of osteophytes and arthroscopic identification of cartilage damage have been reported^{12,34} however, it is unknown if PF osteoarthritis leads to clinical symptoms following cranial cruciate ligament injury. Potentially, as in people, PF osteoarthritis could be a variable that affects clinical outcome after stabilization surgery.

In a study evaluating femorotibial joint cartilage on second-look arthroscopy following stabilization with a tibial plateau levelling osteotomy, there was progression of cartilage damage in both the medial and lateral joint in dogs with complete cranial cruciate ligament tears and minimal damage with partial tears where the cranial cruciate ligament was left intact.⁶ This is not surprising as the intact stifle

femorotibial mechanics have not been restored by the tibial plateau levelling osteotomy²⁴ and the likely reason why damage ensues. We only had 14 stable stifles in this study and therefore adequate comparisons could not be made; however, these stable stifles did have cartilage lesions identified. In comparison, a report using the CORA-based levelling osteotomy, second-look arthroscopy of the femorotibial compartment resulted in minimal to no cartilage progression at a median of 14 months following surgery.¹⁰ When examining the PF joint compartment, PF kinematics and alignment mechanics post-tibial plateau levelling osteotomy have also not been restored following surgery^{35,36} however, PF contact mechanics in canine cadavers following the tibial tuberosity advancement procedure have been shown to be close to normal with maintenance of a decreased retropatellar force.²⁵ Unfortunately, dorsal plane patellar movement and other stifle instability such as internal rotation were not considered in any of these studies. Information on long-term arthroscopic evaluation of the canine PF joint is lacking in all surgical procedures and further evaluation is needed.

As expected, synovitis was identified in all joints in this study and higher synovitis scores were associated with higher MOCS scores. Synovial inflammation is a well-known component in osteoarthritis and cranial cruciate ligament disease²¹ and is present prior to palpable joint instability.³⁷ In people, joint pain and dysfunction are associated with joints that have synovitis and synovitis is considered a predictive factor for increased rates of cartilage loss.^{38–40} Our results support this association of greater degrees of synovitis with higher cartilage severity scores and the important role inflammation plays in the development and progression of osteoarthritis.

A few limitations exist in this study. The main limitation, discussed previously, is the potential for observer variability of the cartilage and synovial scoring systems.²⁰ We attempted to remedy this by using the same, experienced observer to score all articular surfaces; however, observer variability was shown to occur most frequently in the middle scores of the MOCS and this is where the majority of the cartilage scores resided in this study.²⁰ Another limitation was that the observer was not blinded to the clinical presentation of the dog as the observer was also the surgeon performing the arthroscopy. We attempted to decrease bias by having the observer grade the cartilage and synovium at a time point later than surgery without patient identifying information. In addition, the chronicity of cranial cruciate disease at the time scoring was not evaluated; therefore, the severity of cartilage changes may vary depending on the length of time from the onset of the disease and surgical intervention. Lastly, when examining synovitis, we only chose one location, the supratrochlear joint pouch, and there potentially could be variation in the degree of synovitis depending on the site examined.

In summary, arthroscopic articular cartilage lesions are common in dogs with cranial cruciate ligament disease at the time of surgical intervention and the severity of cartilage damage is mild. Additionally, the proximal trochlear groove location in the PF compartment had the most severe cartilage

lesions in the stifle joint. It is unknown how the cartilage at this location will change throughout the progression of the disease. Defining articular cartilage changes early in the disease process is instrumental to understand the progression of osteoarthritis following surgical procedures. Further arthroscopic studies examining cartilage health in the long-term are needed to help determine clinical outcome.

Authors' Contributions

K.A. contributed to the conception of study, study design, acquisition of data and data analysis and interpretation. K.H. contributed to the conception of study, study design and data analysis and interpretation. D.B. contributed to conception of study, and data analysis and interpretation. All authors drafted, revised and approved the submitted. They are publically accountable for relevant content.

Conflict of interest

None declared.

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