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Comparison of biologic scaffolds for augmentation of partial rotator cuff tears in a canine model

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Background: This study was designed to test the hypothesis that biologic scaffold augmentation of articular-sided partial-thickness supraspinatus tendon tears would be associated with superior functional, imaging, biomechanical, and histologic properties compared with untreated tears in a preclinical canine model.

Methods: With Institutional Animal Care and Use Committee approval, dogs (n = 16) underwent half-thickness resection of the articular portion of the supraspinatus tendon (SST). Defects were treated by débridement (DB) (n = 8) or scaffold augmentation on the bursal side using amnion matrix cord scaffold (AM) (n = 8), decellularized human dermal allograft (AF) (n = 8), or bovine collagen patch (RMP) (n = 8). Control dogs (n = 4; 8 normal shoulders) were included. Assessments included lameness, function, comfortable shoulder range of motion (CROM), pain, ultrasonography, magnetic resonance imaging (MRI), arthroscopy, gross examination, biomechanical testing, and histopathology.

Results: At 3 months, CROM was significantly lower and pain significantly higher in DB compared with all other groups. At 6 months, CROM was significantly lower and pain significantly higher in RMP compared with AM and AF, and AM and AF showed significantly less thickening than DB and RMP. AF had the least severe MRI pathology and AM had significantly less MRI pathology than DB. AF SSTs and biceps tendons showed the least severe histopathology, and AM SSTs showed significantly less histopathology than DB and RMP SSTs.

Conclusion: Biologic scaffolds can be effective in augmenting healing of articular-sided partial-thickness SST tears when compared with débridement in a preclinical canine model. Decellularized human dermal allograft and amnion matrix cord may have advantages over the bovine collagen patch for use in this indication.

Level of evidence: Basic Science Study; In Vivo Animal Model

Keywords: Rotator cuff; supraspinatus; scaffolds; animal model; canine

This canine study was conducted under approval from the University of Missouri's Institutional Animal Care and Use Committee (#9334).

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Partial-thickness tears of the rotator cuff are caused by intrinsic and extrinsic factors, and they increase in prevalence with age. After injury, tear enlargement typically occurs with up to 28% becoming full-thickness tears at a year after initial diagnosis.[33] Nonoperative treatment has

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been established as first-line therapy for pain reduction and rotator cuff strengthening in symptomatic patients. This treatment can be effective for approximately one-half of patients.[14,20] If patients continue to have symptoms of pain or loss of motion in spite of appropriate physical therapy, surgical treatment is indicated. Various techniques—from tear débridement to tendon repair—have been described.[15,18,28,32]

The majority of symptomatic partial-thickness rotator cuff tears are partial-thickness articular-sided supraspinatus tendon avulsion (PASTA) lesions. Best current evidence supports repair of symptomatic partial tears in which >50% of the tendon thickness (Ellman grade 3) is affected.[24] However, in addition to thickness criteria, tendon quality remains a factor in treatment indications for rotator cuff tears and impacts outcomes. Tendinosis, thinning, and delamination of tendons threaten the integrity of repair. As such, augmentation of rotator cuff repairs with various scaffolds has been used to enhance the healing environment, improve the mechanical properties of the native tendon, and increase the strength of the suture-tendon interface.[8,22] Synthetic,[29] xenograft dermis[5] and intestinal submucosa,[13,21] allograft tendons, and acellular dermal matrices are scaffolds that have been used for this purpose with varying degrees of success.

These scaffolds have primarily been used for augmentation of complete rotator cuff tendon repairs with acellular dermal matrices reported to be associated with excellent handling characteristics, appropriate biomechanical properties, and favorable clinical outcomes.[3,4,22] Newer scaffolds, including bioinductive bovine collagen and amnion derived membranes,[17,25] have characteristics that may further improve tendon quality and patient outcomes. As such, use of these scaffolds to augment partial tears in an overlay fashion has been described.[25,30] Ideally, partial thickness tears could be treated in this manner without disrupting the native insertion to reliably restore tendon integrity and function. However, the ideal method for accomplishing this goal has not been determined to date, and there is no strong consensus regarding the optimal treatment of these PASTA lesions.

A major limitation for developing and validating an optimal solution for this common clinical problem is the inability to perform comprehensive longitudinal assessments that include functional, diagnostic imaging, and invasive basic science outcome measures in patients. To overcome this limitation, a preclinical large animal model is necessary to include clinically applicable surgical techniques and outcome measures such as arthroscopy, standard-of-care ultrasonographic and magnetic resonance imaging (MRI), and functional assessments including measure of pain and comfortable range of motion. Several biologic scaffolds have been tested in preclinical large animal models for rotator cuff repair.[9-11,19,26,27] However, previous studies have primarily focused on full-thickness defects of the infraspinatus tendon such that no preclinical large animal model for partial-thickness articular-sided supraspinatus tendon (SST) tears has been reported in the peer-reviewed literature to the authors' knowledge.

Therefore, the objectives of the present study were (1) to develop a valid preclinical large animal (canine) model for the study of articular-sided partial-thickness rotator cuff tendon (supraspinatus) tears, and (2) to test biologic scaffolds designed for soft tissue augmentation of repairs for these tears using comprehensive longitudinal outcome measures. The present study was designed to test the hypothesis that bursal-sided biologic scaffold augmentation of articular-sided partial-thickness SST tears would be associated with superior functional, diagnostic imaging, biomechanical, and histologic properties when compared with untreated tears in a preclinical canine model.

Methods

This is a preclinical study using a translational canine model for surgical treatment of articular-sided partial-thickness SST tears. With Institutional Animal Care and Use Committee approval, skeletally mature (2-3 years of age, mean weight = 22 kg; Marshall Farms BioResources, North Rose, NY, USA; 145 USDA #21-A-008) purpose-bred dogs (n = 16) with radiographically and clinically normal shoulders were premedicated, anesthetized, and prepared for aseptic surgery of both shoulders (n = 32). Through a 4-cm cranio(antero)lateral incision over the distal scapula and proximal humerus, the SST was identified and isolated through the lateral rotator interval. The tendon thickness was measured at its midpoint (mean = 7.6 mm; range, 6.5-8.5 mm), and a half-thickness resection (mean = 3.7 mm; range, 3-4 mm) of the articular portion with elevation of the proximal footprint of the SST was performed using a #10 scalpel blade.[24,33] The thickness and area of resection were measured and recorded. Based on random-order assignment, the treatment of the defect was performed as follows using commercially available scaffolds with preclinical and/or clinical evidence for safety and potential efficacy for the treatment of rotator cuff tendon pathology (Fig. 1):

- Débridement (DB) (n = 8): the defect was left untreated and 6 simple interrupted sutures (2-0 Fiberwire; Arthrex, Inc., Naples, FL, USA) were placed around the periphery of the defect on the bursal side of the SST.
- Amnion matrix cord scaffold (Arthrex Amnion [AM]) (n = 8): an AM implant (Arthrex, Inc.) was trimmed to match the dimensions of the defect, placed epithelial side up on the bursal side of the SST, and stabilized to the tendon using 6 simple interrupted sutures (2-0 Fiberwire) placed around the periphery of the defect.
- Decellularized human dermal allograft (ArthroFLEX [AF]) (n = 8): a 1-mm-thick AF patch (Arthrex, Inc./LifeNet Health, Virginia Beach, VA, USA) was trimmed to match the dimensions of the defect, placed reticular/dermal side down on the bursal side of the SST, and stabilized to the tendon using 6 simple interrupted sutures (2-0 Fiberwire) placed around the periphery of the defect.
- Bovine collagen patch (Rotation Medical patch [RMP]) (n = 8): an RMP (Smith & Nephew, London, UK) was trimmed to

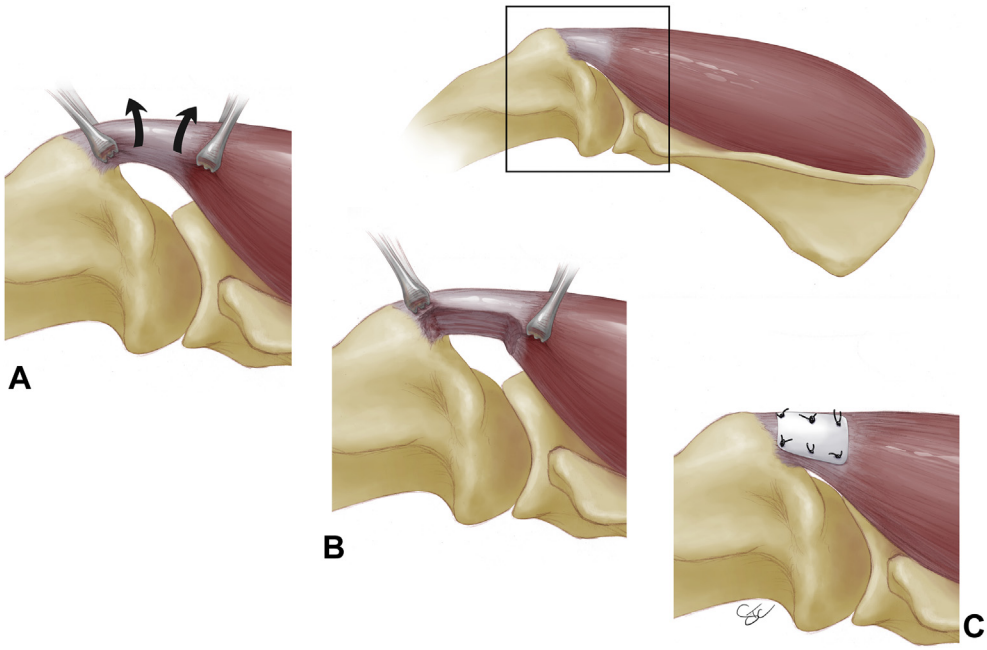

Figure 1 Illustration of surgical procedure performed showing (**A**) the supraspinatus tendon (SST) isolated through the lateral rotator interval, (**B**) half-thickness resection of the articular portion with elevation of the proximal footprint of the SST, and (**C**) bioscaffold sutured on the bursal side of the SST. Reproduced with permission from The Curators of the University of Missouri (copyright 2020 by The Curators of the University of Missouri). Illustration by Stacy Cheavens, MS, CMI.

match the dimensions of the defect, placed with the marking up on the bursal side of the SST, and stabilized to the tendon using 6 simple interrupted sutures (2-0 Fiberwire) placed around the periphery of the defect.

The lateral rotator interval was repaired with 2-0 polydioxanone sutures and the surgical incisions were closed routinely. The dogs were recovered from anesthesia. Analgesics were provided for at least 3 days after surgery and then as needed based on physical parameters indicating the presence of pain. Antibiotics were provided for 10 days per Institutional Animal Care and Use Committee protocol and standard of care for veterinary orthopedics. The dogs were housed in individual kennels with monitoring of daily out-of-kennel exercise and enrichment for the entire study period. The dogs were assessed for any evidence of complications throughout the study period and humanely euthanized by an intravenous dose of sodium pentobarbital at either 3 months (n = 10 dogs; 20 shoulders, n = 5 per treatment group) or 6 months (n = 6 dogs; 12 shoulders, n = 3 per treatment group) after surgery. Age- and breed-matched purpose-bred dogs (n = 4) (Marshall Farms BioResources, North Rose, NY, USA; 145 USDA #21-A-008) with radiographically and clinically normal shoulders (n = 8) that were part of another Animal Care and Use Committee–approved study that did not involve the forelimbs served as controls.

Outcome measures

Before surgery and at 3 and/or 6 months after surgery, lameness grade, level of forelimb function at a trot, comfortable shoulder range of motion (CROM), and visual analog scale (VAS) pain scores were assessed and recorded as previously described.[26,27] Briefly, lameness grades were determined for each dog based on visual examination of gait by a board-certified veterinary orthopedic surgeon using a 10-cm VAS and a validated grading system: 0—no observable lameness; 1—intermittent, mild weight-bearing lameness with little, if any, change in gait; 2—moderate weight-bearing lameness, obvious lameness with noticeable gait change; 3—severe weight-bearing lameness, ''toe-touching'' only; 4—non–weight-bearing. Level of pain was assessed by a board-certified veterinary orthopedic surgeon blinded to time point and treatment using a 10-cm VAS by manually flexing and extending each shoulder individually and observing the dog's behavioral responses from no evidence of pain (0 = no apparent response) to evidence of worst possible pain (10 = extreme vocalization and/or attempt to bite). Shoulder CROM was measured using a standard goniometer with one arm placed along the lateral axis of the spine of the scapula and the other arm placed along the lateral axis of the humerus with the hinge point centered over the shoulder joint line. The shoulder was then manually extended to the highest angle the dog tolerated without showing resistance or pain to determine and record the extension angle (degrees). The shoulder was then manually flexed to the most acute angle the dog tolerated without showing resistance or pain to determine and record the flexion angle (degrees). The flexion angle was subtracted from the extension angle to determine CROM for each shoulder.

Before surgery and at 6 weeks, 3 months, and/or 6 months after surgery, ultrasonographic assessments of the study dogs as well as age- and breed-matched normal control dogs (n = 4 dogs, 8 shoulders) were performed to evaluate the SST appearance and integrity, and the presence of biceps impingement. The procedure was performed using a GE LOGIQ e with a 12 MHz linear array transducer (GE Healthcare, Wauwatosa, WI, USA), and the ultrasonographer was blinded to treatment.

At the 3-month or 6-month endpoint, MRI, arthroscopic assessment, gross examination, biomechanical testing, and histologic evaluations were performed as previously described.[6,7,26,27]

Briefly, MRI was performed on each shoulder using a 3 Tesla MRI (Titan3T; Canon Medical Systems USA, Inc., Tustin, CA, USA) and a spine coil using the following sequences: sagittal T2, sagittal T2 with fat saturation, sagittal proton density fat saturation, coronal T2, corononal proton density, and axial proton density. The MRI was read by a musculoskeletal radiologist blinded to treatment and assessed using a categorical grading system[27] for proximal humerus (0-3: normal = 0, mild bone marrow lesion [BML] = 1, moderate BML = 2, severe BML = 3), tendon-bone junction (0-3: normal = 0, fully attached but not normal junction = 1, partially attached = 2, completely unattached = 3), tendon (0-3: normal = 0, intact with edema/irregularity = 1, partial tearing and/or abnormal tissue architecture = 2, complete tear and/or severely abnormal tissue architecture = 3), and muscle (0-3: normal = 0, mild atrophy = 1, moderate = 2, severe atrophy and/or degenerative changes and/or fatty infiltration = 3). The categorical scores were summed to determine the total MRI pathology score and used for comparison between groups.

Shoulders were then examined arthroscopically using a 3.0-mm 30° foreoblique scope through a caudo(postero)lateral portal to subjectively assess the articular cartilage, biceps tendon, synovium, SST, and lateral glenohumeral ligament.[6,7]

The forequarters were then removed from the dog and the SST scapula-muscle-tendon-proximal humerus complex was excised en bloc and photographed. The humerus was secured in a custom-designed jig and the scapula was attached to the test machine ram by use of a jaw clamp to allow for nondestructive tensile loading along the anatomic vector of SST contraction.[26,27] The SSTs were loaded in tension at a displacement-controlled rate of 0.01 mm/s. Loads at 2, 5, and 10 mm of displacement were extracted from the load vs. displacement curve of each sample. Stiffness was calculated by use of the gradient of the respective force-displacement curves.

After nondestructive biomechanical testing, specimens for histology were harvested and placed in 10% neutral buffered formalin. After fixing, the humerus-tendon-muscle complex for each specimen was trimmed and placed in 10% ethylenediaminetetraacetic acid solution (pH 7.2-7.4) with constant agitation for approximately 2-4 weeks. After complete decalcification of bone (ie, bone was pliable) and softening of the tendon, the specimens were histologically processed routinely and 5-μm-thick longitudinal sections were cut and stained with hematoxylin and eosin and toluidine blue for histologic examination. These sections were subjectively assessed with light and polarized light microscopy by 2 board-certified veterinary pathologists blinded to treatment. Histologic grading was performed based on the updated Bonar scoring system.[12] For each assessment, treated groups were compared with age- and breed-matched normal controls.

Statistical analyses

Analyses were performed using a computer software program (Sigma Stat; Systat Software, Inc., San Jose, CA, USA). Data for each group were combined and means ± standard deviations were calculated. Continuous data were compared among groups using a 1-way analysis of variance. Categorical data were compared among groups using a 1-way analysis of variance on ranks. Statistical significance was defined a priori as $P < .05$.

Results

All dogs underwent all surgical procedures and survived for the intended duration of the study with only mild transient incisional seroma formation noted as a relative complication in all shoulders. No clinical signs of infection, dehiscence, or implant problems were noted in any dog. Neither lameness nor dysfunction was noted for either forelimb of any dog at any assessment time point. At 3 months, all treatment groups had significantly ($P = .033$ or less) lower CROM and significantly ($P = .044$ or less) higher VAS pain scores compared with controls with no statistically significant differences among treatments. However, CROM was significantly ($P = .019$ or less) lower and VAS pain scores were significantly ($P = .026$ or less) higher in the DB group compared with all other groups and in the RMP group compared with the AM and AF groups at the 6-month time point (Table I).

Ultrasonographic assessments

Longitudinal ultrasound assessments revealed that untreated (DB) SSTs did not all remain completely intact based on ultrasonographic appearance with 1 (12.5%) and 4 (50%) not fully intact at 6 weeks and 3 months, respectively. However, at 6 months after surgery, all remaining untreated SSTs had tissue bridging the defect

Table I Pain and function scores

Group	Lameness (0-4)			Function (0-10)			Pain (0-10)			CROM (degrees)		
Time point	Pre	3 mo	6 mo	Pre	3 mo	6 mo	Pre	3 mo	6 mo	Pre	3 mo	6 mo
Control	0 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0	0 ± 0[a]	0 ± 0[a]	125 ± 3	124 ± 3[a]	124 ± 4[a]
DB	0 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0	1.1 ± 0.5[b]	1.6 ± 0.5[b]	124 ± 3	113 ± 5[b]	103 ± 6[b]
AM	0 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0	0.7 ± 0.7[b]	0.1 ± 0.1[a]	125 ± 2	118 ± 7[b]	123 ± 1[a]
AF	0 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0	0.2 ± 0.4[b]	0.1 ± 0.1[a]	124 ± 2	120.9 ± 5[b]	123 ± 2[a]
RMP	0 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0	0.8 ± 0.6[b]	0.7 ± 0.1[c]	126 ± 3	114 ± 7[b]	117 ± 2[c]

DB, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch; *CROM*, comfortable range of motion.
Note: different letters denote statistically significant differences for groups within each column. Statistical significance was defined as $P < .05$.

Table II Ultrasonographic assessments

Group	Thickness (mm)			Width (mm)			Tendon abnormalities			Biceps impingement		
	6 weeks	3 mo	6 mo	6 weeks	3 mo	6 mo	6 weeks	3 mo	6 mo	6 weeks	3 mo	6 mo
Control	7.3 ± 0.3			9.5 ± 0.5			Nrm (4)			None (4)		
DB	10.4 ± 4.1	10.0 ± 2.2	10.7 ± 2.3	14.8 ± 5.4	14.9 ± 4.2	12.5 ± 2.1	Mod (4) Sev (4)	Mod (5) Sev (3)	Mild (1) Sev (2)	Mod (5) Sev (3)	None (2) Mild (4) Mod (2)	Mild (3)
AM	8.4 ± 2.8	9.0 ± 1.0	7.8 ± 0.4[a]	13.3 ± 2.2	11.7 ± 2.6	10.4 ± 1.2	Mod (6) Sev (2)	Nrm (1) Mild (4) Mod (3)	Nrm (1) Mild (2)	Mild (5) Mod (3)	None (6) Mild (2)	None (2) Mild (1)
AF	9.3 ± 1.6	8.4 ± 1.1	7.6 ± 0.3[a]	13.1 ± 3.4	10.6 ± 1.5	11 ± 1.7	Nrm (1) Mild (4) Mod (3)	Nrm (4) Mild (4)	Nrm (1) Mild (2)	Mild (5) Mod (3)	None (7) Mild (1)	None (3)
RMP	10.9 ± 1.6	10.4 ± 2.1	11.1 ± 3.1	16.5 ± 5.1	15.8 ± 4.1	11.7 ± 1.2	Sev (8)	Nrm (1) Mild (2) Sev (5)	Mild (1) Mod (1) Sev (1)	Mild (4) Mod (3) Sev (1)	None (4) Mild (4)	None (1) Mild (2)

DB, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch; *Nrm*, normal; *Mod*, moderate; *Sev*, severe.
Note: Different letters denote statistically significant differences for groups within each column. Statistical significance was defined as $P < .05$.

site. Débrided SSTs remained thickened compared with controls with notable ultrasonographic-evident abnormalities and ultrasonographic evidence for biceps impingement at all time points. RMP-treated SSTs also remained thickened compared with controls with notable ultrasonographic-evident abnormalities and biceps impingement at all time points. However, the nature of the ultrasonographic abnormalities differed between the DB and RMP groups. DB-associated abnormalities were related to inhomogeneous echogenicity with loss of linear striations indicative of unorganized connective tissue, whereas RMP-associated abnormalities consisted of peritendinous fluid accumulation and hyperechoic, thickened tissues indicative of a foreign body response with inflammation and synovitis. AM-treated and AF-treated SSTs showed similar ultrasonographic findings throughout the study period with a progressive decrease in tissue thickness, a decrease in echogenicity, and realignment of fibers indicative of tendon healing and remodeling. The only statistically significant differences among groups were for tendon thickness at 6 months after surgery at which point AM-treated and AF-treated SSTs were significantly ($P = .038$ or less) thinner than DB-treated and RMP-treated SSTs. Thicknesses of AM-treated and AF-treated SSTs were not significantly different from controls at the 6-month time point (Table II).

MRI

MRI revealed tissue bridging the SST defect site in all groups at both time points. However, 4 of the DB SSTs showed partial discontinuity at the 3-month time point. Hyperintense peritendon, intramuscular, and intra-articular fluid was noted in all groups at the 3-month time point. The amount of fluid decreased over time but remained prominent in the RMP group with fluid noted within and around the SST scaffold. Some degree of impingement of the intra-articular portion of the biceps tendon by SST-associated tissues was noted in all groups at 3 months with the greatest number and severity in the DB and RMP groups. Biceps impingement decreased by 6 months after surgery with complete resolution in the AF group and highest number and severity in the DB and RMP groups. No BMLs at the SST insertion on the greater tubercle, or elsewhere, were noted for any group at either time point. All groups showed progressive healing and remodeling of SSTs from 3 to 6 months. AM-treated and AF-treated SSTs had similar appearance on MRI with tendon fibers approaching normal intensity, thickness, and cross-sectional area at the 6-month time point. MRI pathology scores were significantly ($P = .048$ or less) different among groups at the 6-month time point at which time AF-treated SSTs showed the least severe pathology. AM-treated SSTs were scored as having significantly less pathology than DB-treated SSTs. No other differences were statistically significant (Fig. 2, Table III).

Arthroscopy

Subjective arthroscopic assessments showed varying degrees of synovitis, adhesions, fibrosis, and biceps tendon impingement among groups and time points. In general, these abnormalities were most severe in the DB group at 3 months after surgery and least severe in the AM and AF groups at 6 months after surgery. However, no statistically significant differences were noted (Fig. 3).

Gross appearance

Grossly, all SSTs were partially to fully intact at each time point. Patch-defect location could be identified by the

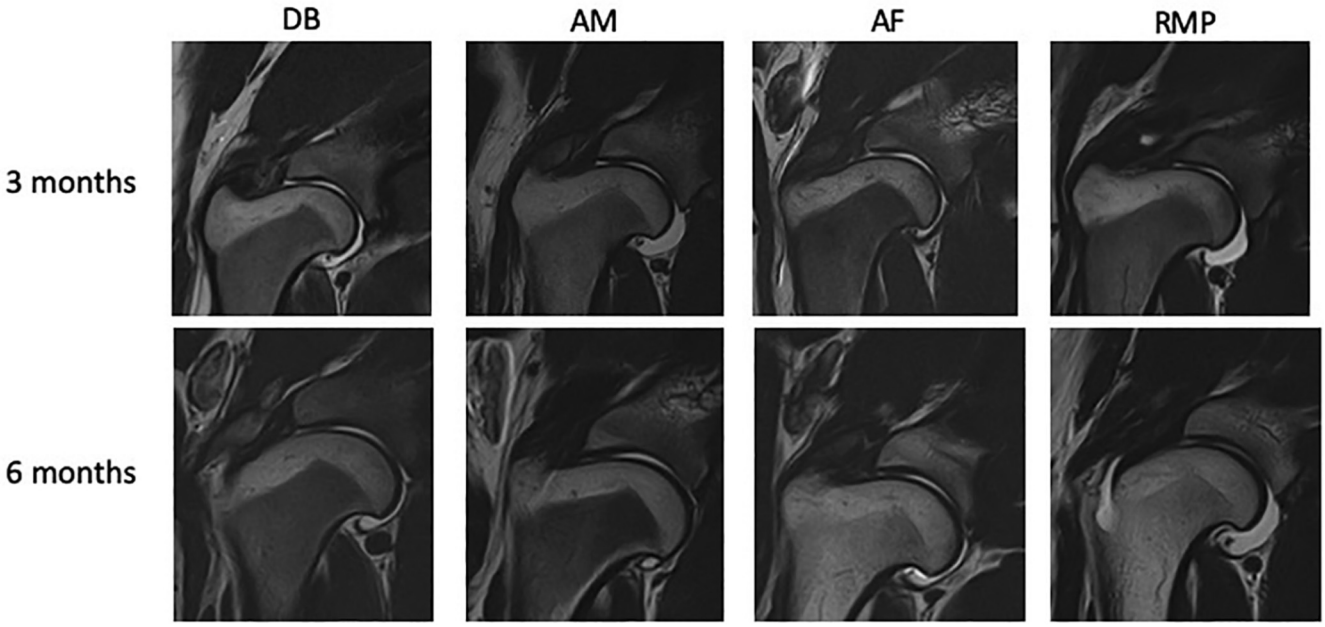

Figure 2 Representative T2-weighted magnetic resonance images of the shoulders of dogs in the present study at 3 (top row) or 6 months (bottom row) after the treatment of surgically created partial-thickness supraspinatus tendon defects. *DB*, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch.

presence of the peripheral sutures in all shoulders. Bridging tissue was least robust in the DB group at 3 months. Prominent hypervascularity and inflammatory tissue was noted in association with all RMP-treated SSTs. SSTs in the AM and AF groups were intact without evidence of prominent hypervascularity or inflammation (Fig. 4).

Biomechanical testing

No statistically significant differences were noted among groups at either time point for loads to 2, 5, or 10 mm of displacement or for SST-construct stiffness (Fig. 5).

Histology

Histopathology scores for SSTs and biceps tendons were significantly ($P = .045$ or less) different among groups at the 6-month time point at which time AF-treated SSTs and biceps tendons showed the least severe pathology. AM-treated SSTs and biceps tendons were scored as having significantly less pathology than for the DB and RMP groups. No other differences were statistically significant. Histologic changes in SSTs that were consistent across all treatment groups included diffuse hypercellularity with some alteration in tenocyte morphology (rounded phenotype), increased ground substance, mild fatty infiltration at the musculotendinous junction, mild synovial hyperplasia, and mild fibrosis at the tendon-bone attachment site at the 3-month time point, and similar findings at the 6-month time point with the addition of small areas of focal necrosis as well as varying degrees of fibrosis (Fig. 6). Subjective histologic differences among groups were related to tendon defects, synovial hyperplasia (Fig. 7, *A*), and the

Table III Magnetic resonance imaging and histology results

Group	SST MRI (0-15)				SST histology (0-15)				Biceps histology (0-15)			
Time point	3 mo		6 mo		3 mo		6 mo		3 mo		6 mo	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
DB	11.9	9-14	7.0[a]	5-9	11.2	9-13	7.8[a]	4-9	8.6	7-11	4.3[a]	2-7
AM	9.2	7-11	4.0[b,c]	2-6	9.6	6-11	3.7[b,c]	2-6	7.0	5-9	1.6[b]	1-3
AF	9.0	6-11	3.5[b]	1-5	9.8	7-11	3.4[b]	2-5	7.4	6-9	1.0[b]	0-2
RMP	12.6	10-14	6.5[a,c]	4-9	12.4	8-13	5.9[a,c]	3-8	9.8	7-12	4.0[a]	2-6

DB, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch; *SST*, supraspinatus tendon; *MRI*, magnetic resonance imaging.
Note: Different letters denote statistically significant differences for groups within each column. Statistical significance was defined as $P < .05$.

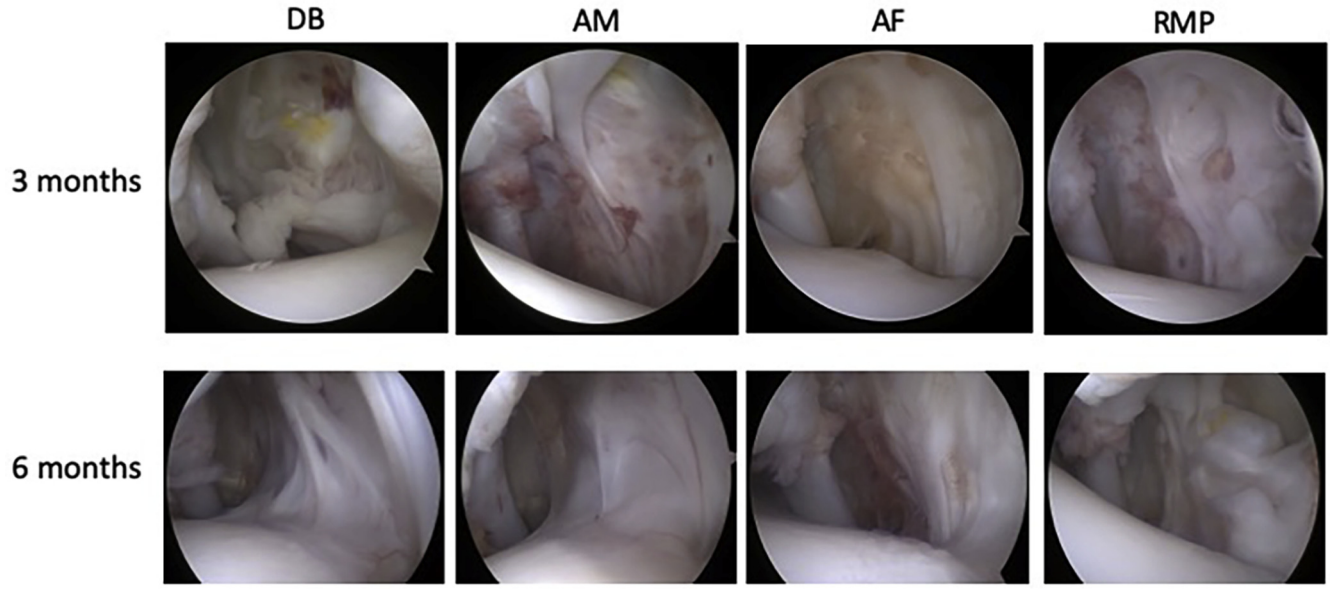

Figure 3 Representative arthroscopic images of the anterolateral compartment of the shoulders of dogs in the present study at 3 (top row) or 6 months (bottom row) after the treatment of surgically created partial-thickness supraspinatus tendon defects. *DB*, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch.

nature of the foreign body reaction (Fig. 7, *B*). Histologic changes in biceps tendons that were consistent across all treatment groups included mild hypercellularity with some alteration in tenocyte morphology (rounded phenotype), increased ground substance, and mild-to-moderate synovial hyperplasia at both the 3- and 6-month time points. Subjective histologic differences among groups primarily related to the degree of synovial hyperplasia were noted (Fig. 7, *C*; Table III).

Discussion

The results from the present study allowed us to accept the hypothesis in that bursal augmentation of articular-sided partial-thickness SST tears using amnion matrix cord, decellularized dermal, or bovine collagen derived scaffolds was associated with superior functional, diagnostic imaging, and histologic properties when compared with untreated defects in a preclinical canine model. All 3 biomaterial scaffolds protected the partially resected SSTs

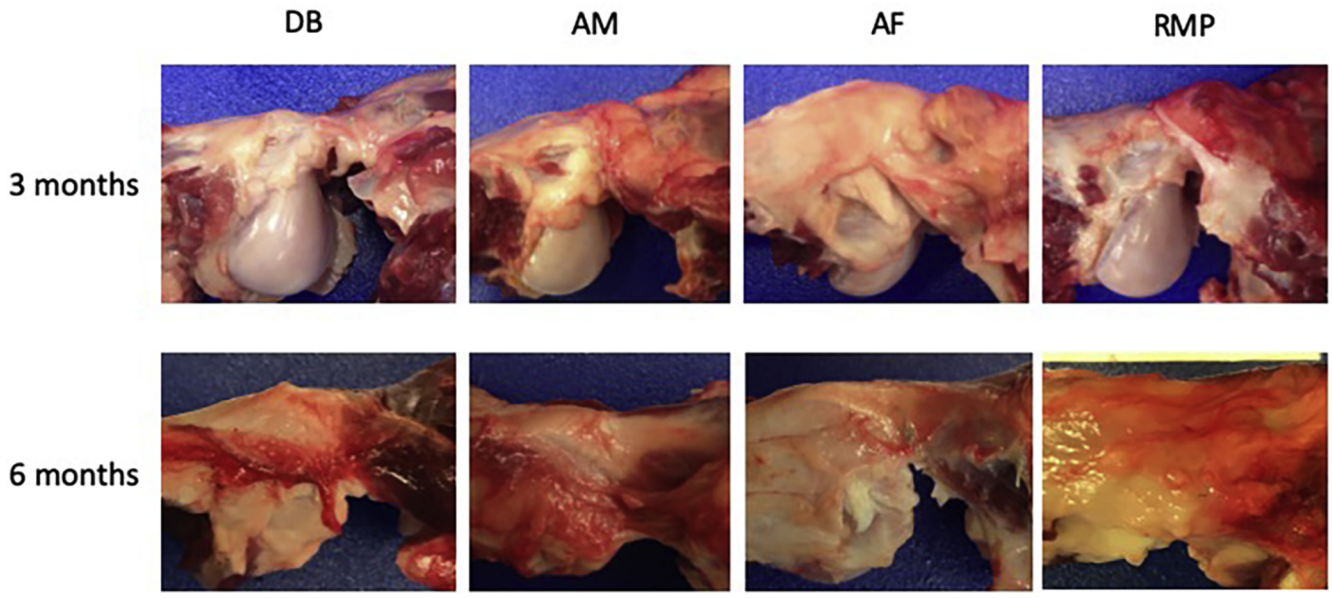

Figure 4 Representative gross images of the dissected shoulders of dogs in the present study at 3 (top row) or 6 months (bottom row) after the treatment of surgically created partial-thickness supraspinatus tendon defects. *DB*, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch.

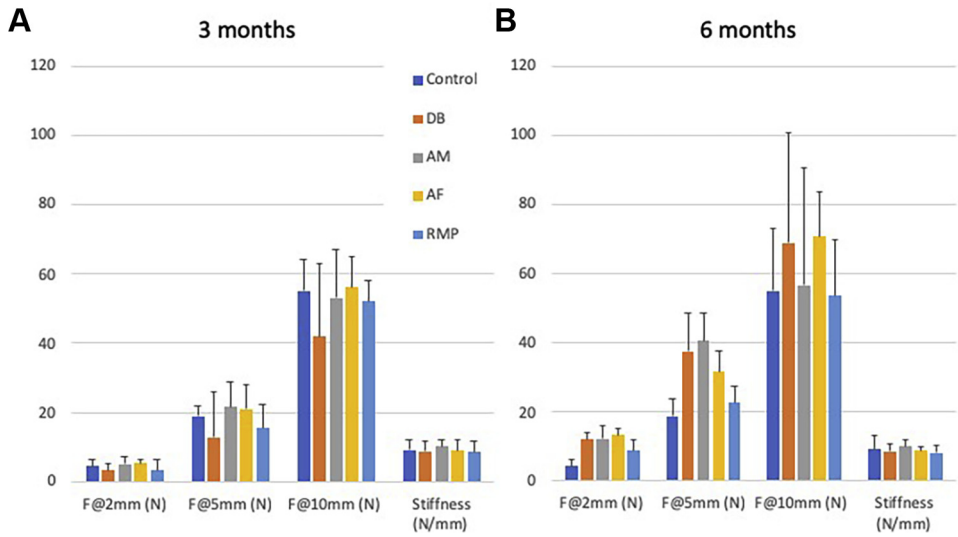

Figure 5 Mean ± standard deviation force (N) and stiffness (N/mm) values for load-to-displacement testing of supraspinatus tendons at 3 (**A**) or 6 months (**B**) after the treatment of surgically created partial-thickness supraspinatus tendon defects. *DB*, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch.

through 6 months postoperatively in terms of maintaining an intact tendon that did not fail through 10 mm of tensile loading. However, there were no differences in biomechanical properties tested when scaffold-treated SSTs were compared with debrided SSTs. In addition, none of the scaffolds were able to completely restore the native tendon structure and architecture within the 6-month study period. Interestingly, there were consistent differences among groups at the 3- and 6-month time points. The débridement group was the least normal with respect to pain, shoulder range of motion, tendon structure and architecture, and biomechanical properties. Decellularized human dermal allograft-treated SSTs were the most normal with respect to pain, shoulder range of motion, tendon thickness, structure and architecture, and biceps tendon pathology. Amnion matrix cord scaffold-treated SSTs were superior to the RMP and DB groups with respect to pain, shoulder range of motion, tendon thickness, structure and architecture, and biceps tendon pathology. Bovine collagen patch–treated SSTs were superior to debrided SSTs with respect to pain and shoulder range of motion, but were consistently associated with hypervascularity,

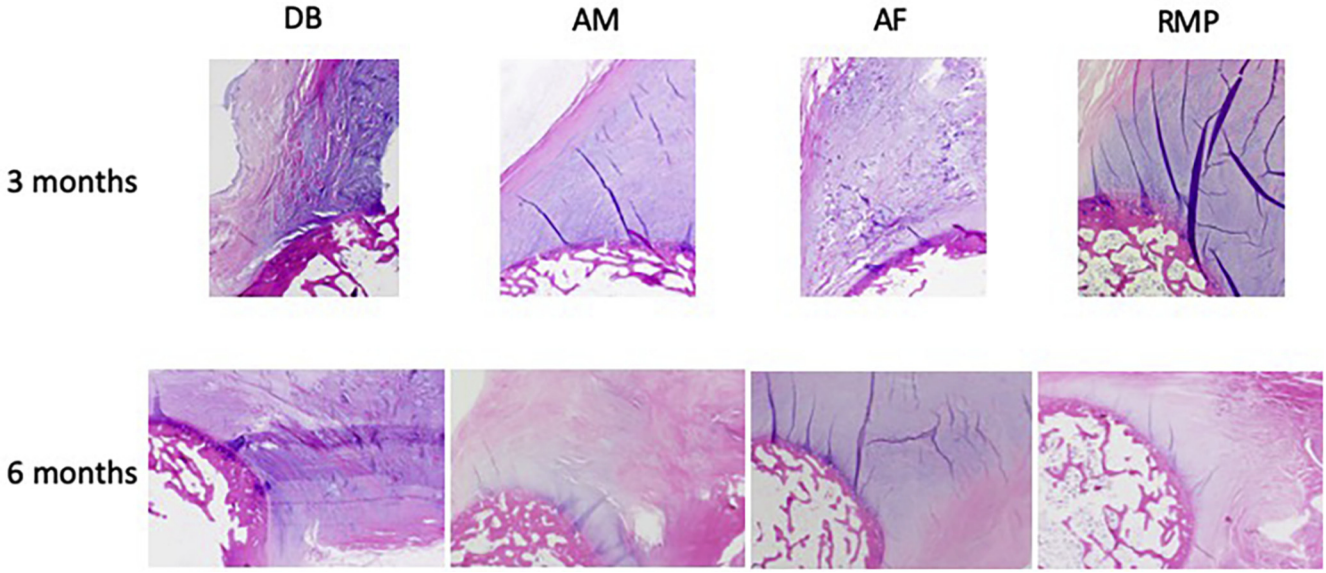

Figure 6 Histologic changes observed in the supraspinatus tendons were consistent across all treatment groups at the 3- and 6-month time points. At low magnification (2× objective), increased ground substance can be seen in the tendon. *DB*, débridement; *AM*, Arthrex Amnion; *AF*, ArthroFLEX; *RMP*, Rotation Medical patch.

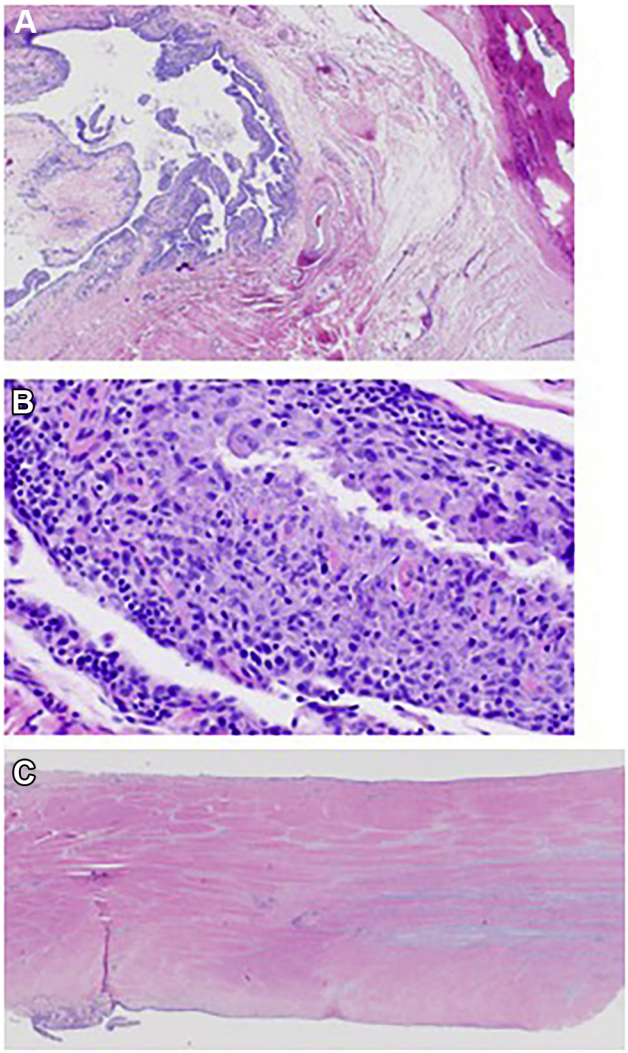

Figure 7 Subjective histologic differences were seen amongst treatment groups related to synovial hyperplasia (**A**) and the presence of the foreign body reaction (**B**). Histologic changes observed in the biceps tendons were consistent across all treatment groups at the 3- and 6-month time points. At low magnification (2× objective), increased ground substance, clusters of capillaries, and synovial hyperplasia can be seen in the tendon (**C**).

inflammatory reactions characterized by an apparent foreign body response and biceps tendon pathology that resulted in diagnostic imaging, gross and histologic changes that were inferior to amnion matrix cord, and decellularized human dermal allograft scaffolds.

Importantly, the model designed for the present study appeared to be an effective large animal model for partial rotator cuff tendon (supraspinatus) tears with clinically applicable outcome measures based on the comparable functional, diagnostic imaging, and arthroscopic outcomes noted.[25,30] The PASTA lesion created in the dogs closely mimicked lesions commonly encountered in patients and the bursal-sided repair was accomplished in a similar manner as the arthroscopic or mini-open approaches used in people. The primary difference in this model compared with the clinical situation is related to the weightbearing status of the canine upper extremity relative to typical rehabilitation protocols for patients. Dogs were allowed immediate use of both forelimbs and only controlled based on housing and exercise restrictions, representing a ''worst case scenario'' for postoperative compliance of patients such that outcomes in this study should be considered as highest demand on the scaffolds. Importantly, the outcomes noted for dogs in the present study closely resembled those reported for patients in terms of fibrous tissue formation, hypervascularity, and maintenance of tendon integrity based on diagnostic imaging.[25,30]

Although each of the scaffolds appeared to have some benefits with respect to encouraging fibrous tissue formation at the SST defect site, the differences among patches are intriguing and have potential clinical importance. The most favorable effects noted in the present study were in conjunction with decellularized human dermal allograft scaffolds. Based on the beneficial effects on pain, shoulder range of motion, and tendon thickness, structure, and architecture associated with this scaffold, it is likely that both biomechanical and biologic mechanisms were involved in the positive effects. This scaffold is the most robust of those studied and, together with the collagen and glycosaminoglycan extracellular matrix,[1] likely conveyed the best combination of properties to augment tendon healing in this preclinical model. The amnion matrix cord scaffold was associated with very similar functional and structural effects on healing SSTs in the present study likely through similar mechanisms, although it is likely that the positive effects may have been more biologically, rather than biomechanically, mediated.[16,23,31] The beneficial structural and functional effects with the absence of inflammatory and proliferative (thickening) responses associated with AF and AM scaffolds likely also account for the more positive intra-articular findings noted in the present study. Although the scaffolds would not be expected to have direct effects on the intra-articular environment, whole-tendon health, structure, and function are dependent on all components of the functional unit. As such, the data suggest that AF and AM treatments restored the whole-tendon functional unit most completely and mitigated related intra-articular pathology. The bovine collagen patch was not associated with the same levels of beneficial effects as the other 2 scaffolds in this study. In addition, a consistent inflammatory, foreign body reaction was noted in association with this scaffold, and was associated with the highest (most abnormal) tendon thickness at endpoint. These differences may be related to the nature of the manufacturing process for this scaffold compared with the others that are naturally occurring scaffolds and/or the species of origin.[30] Although each of these scaffolds would be considered xenogeneic in this canine model, the human vs. bovine origin may be responsible for at least

some of the differences noted. However, a similar foreign body reaction in human patients in association with the bovine collagen patch has recently been reported.[2]

The limitations of the present study must be considered when interpreting and applying the results. The major limitations include the use of a preclinical animal model based on a surgically created defect, the study duration, and the number of animals used. Although the model used an experimental defect in dogs, the surgically created SST tear mimicked what is commonly encountered in patients and allowed for very consistent defects for comparison across treatments. Importantly, the experimental design also allowed for longitudinal comparisons over a 6-month time period with comprehensive outcome measures including functional, diagnostic imaging, arthroscopic, gross, biomechanical, and histologic assessments such that translational capabilities were optimized. Although the 6-month study period cannot be considered as applicable to the long-term effects of the treatments studied, this period of time in the canine model can be considered valid for assessment of safety and efficacy during the critical post-operative healing, remodeling, and rehabilitation period. In addition, the fact that the animals were allowed full weightbearing on the treated limbs immediately after surgery makes this a very stringent test of the interventions evaluated. Finally, although the number of dogs used was minimized to adhere to the 3 R's of ethical animal research (replacement, reduction, and refinement), the ability to use bilateral defects without causing undue pain or dysfunction in the dogs allowed for direct comparisons that did reach statistical significance. In addition, the same specimens were used for biomechanical testing and histologic assessments to also comply with most ethical use of animals. Although biomechanical testing may have some effects on the tissues with respect to subsequent histologic assessments, only nondestructive testing was employed and all specimens were tested in the same manner. As such, the data from these 2 critical outcome measures are derived from the same specimens, providing more direct relationships for valid structure-function comparisons among treatments.

Conclusion

Taken together, these data suggest that biologic scaffolds can be effective in augmenting healing of articular-sided partial-thickness SST tears when compared with untreated defects in a preclinical canine model. Although all 3 scaffolds tested protected the SST through the initial 6-month healing period and allowed for restoration of its biomechanical properties, none were able to completely restore native tendon structure and architecture within this time period. In addition, there were consistent differences among the scaffolds suggesting that decellularized human dermal allograft and amnion matrix cord may have advantages over the bovine collagen patch for use in this indication. However, further critical evaluation should be performed to determine whether or not these preclinical data are directly applicable to results in patients.

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