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Scaffold and Graft-Based Biologic Augmentation of Rotator Cuff Repair: An Updated Systematic Review and Meta-Analysis for 2010-2022

Albert Mousad, BS, Olivia Bono, BS, Krishna Mandalia, BS, Julianne Forlizzi, MD, Glen Ross, MD, Sarav Shah, MD

Study conducted at New England Baptist Hospital
Boston, Massachusetts, UNITED STATES

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Mousad, A: No Financial Conflicts to Disclose

Bono, O: No Financial Conflicts to Disclose

Mandalia, K: No Financial Conflicts to Disclose

Forlizzi, J: Paid Speaker/Presenter *(DJ Orthopaedics)*

Ross, G: Paid Consultant; Paid Speaker/Presenter *(Arthrex, Inc)*
Paid Consultant; Paid Speaker/Presenter *(Stryker)*

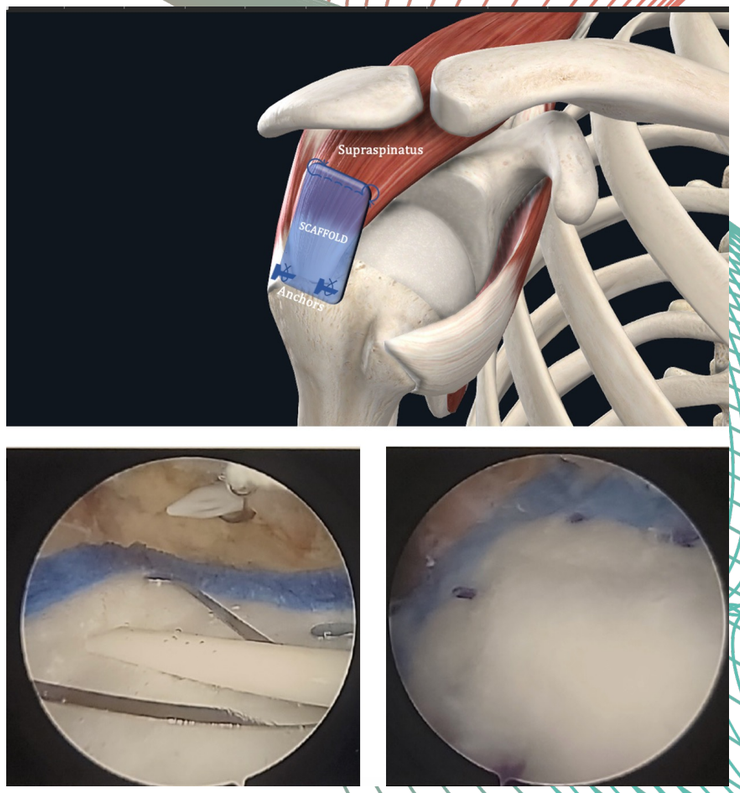
Shah. S: Paid Consultant (*Exactech, Inc*)

Introduction

- Despite advancement in rotator cuff repair [RCR] surgical techniques, retear rates following RCR remain very high, with some studies reporting retear rates between 20% and 94%[3,16,58]
  - Furthermore, intact RCR has been shown to correlate with improved patient reported outcome measures (PROMs),[40] and correlated with lower grades of osteoarthritis at 10 and 20-year follow up.[33,66]
- Failed RCRs pose unique challenges to both patients and orthopaedic surgeons
- Many surgeons agree that the weakest aspect of the modern RCR construct resides in the tissue-suture interface often resulting in suture pull-through.[7,8,23,62]

Purpose

- The past decade has yielded several novel strategies to improve the biological healing of rotator cuff tears via overlay grafts and scaffolds[52]
  - Graft: serving to supplement the strength of the repaired native rotator cuff (*Study Definition*)
  - Scaffold: providing a footprint by which biologic cells adhere and promote healing via induced tendon vascularization and native tissue regeneration (*Study Definition*)
- This study sought to provide a focused, systematic review and meta-analysis of the use of overlay grafts and scaffolds (excluding superior capsule reconstruction) in RCR augmentation in both animal models and human clinical settings.

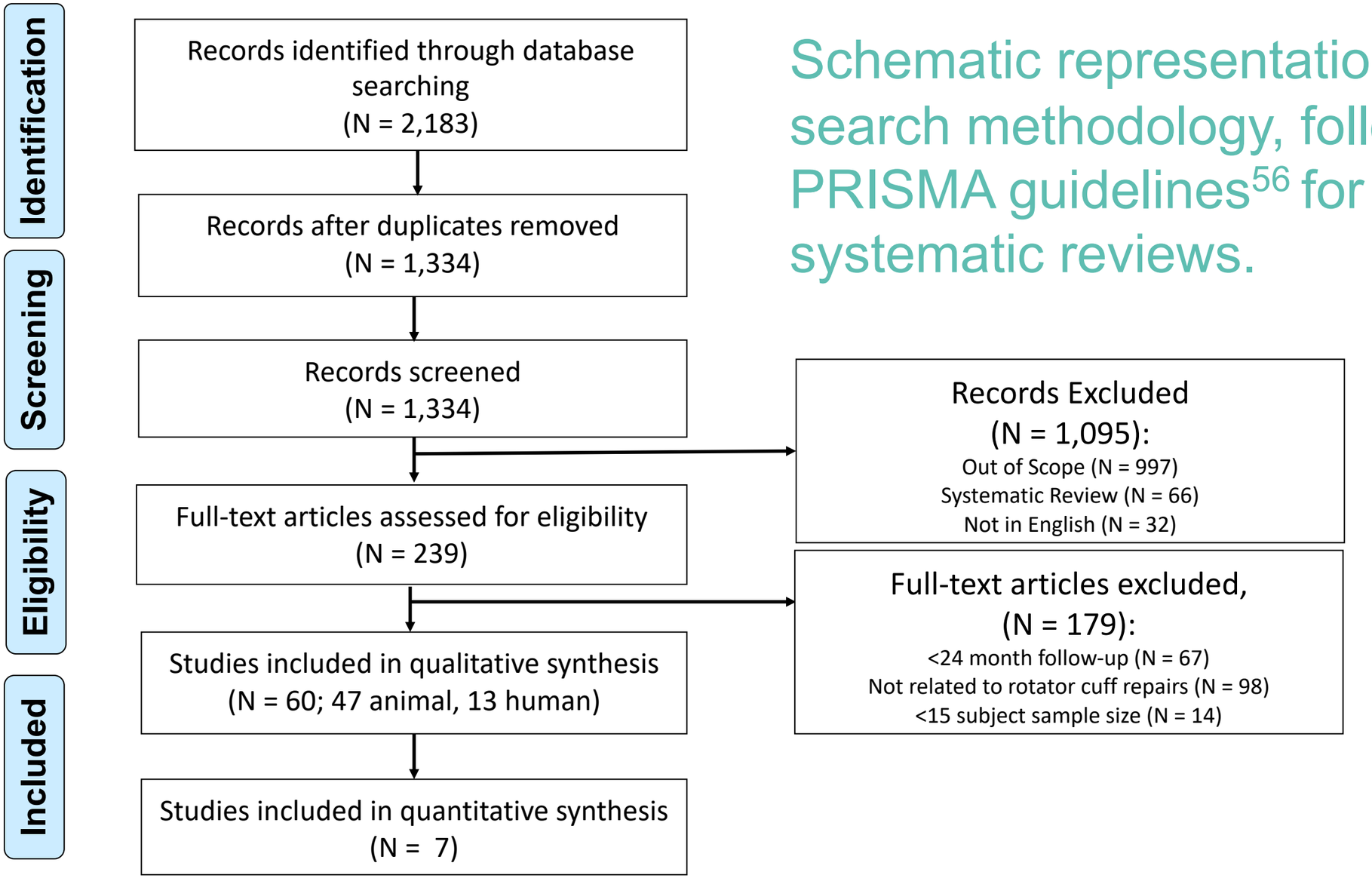


An example of this augmentation scheme with intraoperative images of rotator cuff repair enhanced with resorbable bovine collagen scaffold.

Methods

- Systematic Review was performed according to guidelines via PRISMA[56] and Cochrane Collaboration[22]
- PubMed, Embase, and the Cochrane Library databases were searched for studies related to biologic augmentation of RCR with graft or scaffold in human or animal-models from January 2010 until December 2022
  - Exclusion Criteria: Review articles, systematic reviews, editorials, non-English articles, articles focused on superior capsular reconstruction, studies with less than fifteen subjects and/or less than 24-month follow up
- Methodological quality was assessed using the CLEAR-NPT and MINORS protocols with included studies being of low risk of bias
- Quantitative assessment via meta-analysis of pooled retear rates in comparative human studies was conducted via Cochrane Training Review Manager 5 (RevMan 5)

Schematic representation of search methodology, following PRISMA guidelines[56] for systematic reviews.



Results: Animal Studies (47 studies)

- 43 studied scaffold-based, 4 studied graft-based augmentation
- Four different animal models: rat (26/47, 55.3%), rabbit (14/47, 29.8%), dog (4/47, 8.5%), and sheep (3/47, 6.4%)
- The most common scaffolds utilized were engineered biomaterials (14/43, 32.6%) followed by collagen-based scaffolds (10/43, 23.3%).
  - The scaffolds used in the remaining 19 studies were highly varied.
- 41 of 47 (87.2%) animal-model studies demonstrated positive biomechanical effects in terms of higher ultimate load-to-failure, stiffness, and strength with promising healing rates[2,4,14,17-19, 25,31,32,34,35,38,41,42,44,45,47-49,54,60,61,63,65,67,68,72,74,77,79,85,88,89,91-96]
  - Improved histologic features such as collagen density/orientation, tissue vascularity, and reduced inflammation were also common findings across studies
- Only six of 47 (12.8%) studies demonstrated a negligible effect from the addition of graft or scaffold in animal models[39,76,80-82]
- There were no serious complications or negative effects of augmentation reported in any of the included animal-model studies.

Results: Human Studies (13 studies)

- 7 studied scaffold-based (6 xenografts,[3,6,13,50,69,84] 1 engineered collagen[11]), 6 studied graft-based augmentation (5 acellular dermal allografts,[20,30,46,57,71] 1 engineered polyester[75])
  - Overall, 9 of 13 (69.3%) human studies illustrated improved results with augmentation
  - 6 of 8 (75%) comparative studies demonstrated improvement in post-operative measures (e.g., retear rate, radiographic thickness and footprint, improved PROM) compared to controls.
- Scaffolds: The addition of a xenograft has mixed results regarding efficacy in augmenting RCR, demonstrating the importance of origin and immunogenicity treatment.[24] Importantly, the reported complication rate was low throughout, which is promising for the safety profile of xenograft tissue. Engineered collagen demonstrated lower retear with improved PROMs in early follow-up.
- Grafts: Acellular dermal allograft augmentation was demonstrated as a safe, low-risk option to lower retear rates compared to standard repair. A similar benefit in retear rate and PROMs was seen with polyester patch use.

Overview of Human Scaffold-Based Biologic Augmentation Study Results

Implant Type	First Author	Journal/ Year	Level of Evidence	Subjects (N)	Tear Size	Procedure	Post-Op Imaging	Significant Findings of Intervention Group
porcine dermal (Conexa Reconstructive Matrix)	Avanzi	JSES 2019	II	69	small & medium	arthroscopic	MRI	Lower retear rate (P<.001); higher tendon thickness and footprint coverage at two year follow-up[3]
porcine dermal (Conexa Reconstructive Matrix)	Castagna	Joints 2018	III	70	large	arthroscopic	MRI	Improved Constant score at 24mo (P=.036); subgroup analysis-those retorn on MRI + patch had higher functional scores (P=.0136)[11]
porcine dermal (Conexa Reconstructive Matrix)	Maillot	JSES 2018	II	32	large & massive	open	None	Improved functional scores in patch group versus debridement (P<.001), 1 deep infection and 4 arthrofibrosis in treatment group[49]
porcine small intestine (Restore Orthobiologic Implant)	Bryant	JSES 2016	I	60	medium & large	open	MRA	Relative risk of retear=0.81; 1 deep infection[6]
bovine collagen (REGENETEN)	Schlegel	JSES 2020	IV	33	partial-thickness	arthroscopic	MRI	95% high and 100% intermediate grade had tissue fill in with 1.8 and 1.2mm increased thickness, respectively[65]
bovine collagen (REGENETEN)	Thon	AJSM 2019	IV	23	large & massive	arthroscopic	MRI	96% healing rate; 91% clinical success rate[81]
3D-printed type I collagen	Cai	AJSM 2018	II	104	medium & large	arthroscopic	MRI	Lower retear rate[9]

Overview of Human Graft-Based Biologic Augmentation Study Results

Implant Type	First Author	Journal/ Year	Level of Evidence	Subjects (N)	Tear Size	Procedure	Post-Op Imaging	Significant Findings of Intervention Group
human dermal matrix (ArthroFlex)	Gilot	Arthroscopy 2015	III	35	large & massive	arthroscopic	US	Lower retear rate; higher patient-reported outcome scores[25]
human dermal matrix (ArthroFlex)	Namdari	AJSM 2021	IV	35	NR; revision & primary complex	arthroscopic	MRI	48% retear rate (57% in revisions, 33% in primary), improved functional scores (ASES & SANE) in healed patients compared to retears (P<.05)[56]
human dermal matrix (MegaDerm)	Choi	KSSTA 2022	III	34	large & massive	arthroscopic	MRI	Lower retear rate (5.9%) compared to control (P=.034), no significant improvement in clinical outcomes[18]
extracellular matrix (Conexa/GraftJacket/ Tisssuemend)	Sears	Orthopedics 2015	IV	24	NR; retears	open; revision	MRI/US	63% retear rate[67]
human dermal matrix (CGDerm)	Lee	CiOS 2022	II	43	large	arthroscopic	MRI	Lower retear rate (9.1%) compared to control (P=.034); greater functional patient scores (ASES, P=.047)[44]
polyester patch (Pitch-Patch)	Smolen	JSES 2020	IV	50	large & massive	arthroscopic	CTA/ MRA/US	14% retear rate[72]

MRA, magnetic resonance angiography; CTA, computed tomography angiography; MRI, magnetic resonance imaging; US, ultrasound; NR, not reported; ASES, American Shoulder and Elbow Surgeon; SANE, Single Assessment Numeric Evaluation.

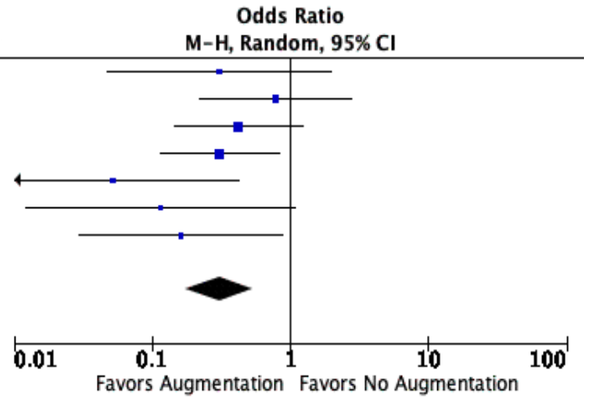
Tables summarizing the study characteristics of the included human studies investigating scaffold-based and graft-based RCR augmentation

Meta Analysis

- Conducted to determine the effect of biologic augmentation of RCR on retear rates. The analysis utilized pooled retear rates from seven comparative human clinical studies.[3,6,11,13,20,30,46]
- Overall, the meta-analysis demonstrated a significantly lower odds of retear in those patients receiving biologic augmentation compared to those without biologic augmentation (P<0.0001).
  - Furthermore, there was relatively low heterogeneity in this analysis (I-squared = 0.09).

	Augmentation		No Augmentation			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Gilot, 2015	2	20	4	15	8.7%	0.31 [0.05, 1.95]	2015
Bryant, 2016	6	34	6	28	17.6%	0.79 [0.22, 2.78]	2016
Catagna, 2018	7	35	13	35	23.3%	0.42 [0.14, 1.24]	2018
Cai, 2018	7	51	18	53	27.2%	0.31 [0.12, 0.82]	2018
Avanzi, 2019	1	41	12	37	6.9%	0.05 [0.01, 0.43]	2019
Choi, 2022	1	17	6	17	6.0%	0.11 [0.01, 1.09]	2022
Lee, 2022	2	22	8	21	10.3%	0.16 [0.03, 0.89]	2022
Total (95% CI)		220		206	100.0%	0.31 [0.17, 0.54]	
Total events	26		67				

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.62$, df = 6 (P = 0.36); $I^2 = 9\%$
Test for overall effect: Z = 4.12 (P < 0.0001)



Conclusions

- Graft and scaffold augmentation have shown favorable results in both pre-clinical and clinical studies.
- Of the investigated clinical grafts and scaffolds, acellular human dermal allograft and bovine collagen demonstrate the most promising preliminary evidence in each category, respectively.
- With a low risk of bias, meta-analysis revealed that biologic augmentation provides increased integrity of RCR, significantly reducing the odds of retear.
  - Since the effects of retear have been widely studied, and have been shown to lead to worse clinical outcomes,[28,33,42] payors may consider collaborating with surgeons to leverage these therapeutic advancements as a cost-effective strategy[64] to improve clinical outcomes and decrease the risk of osteoarthritis.
- Although further investigation is warranted, these findings suggest graft/scaffold biologic augmentation of RCR to be safe.

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