

Scaffolds based therapy for osteochondral lesions of the talus: A systematic review

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Abstract

AIM

To clarify the effectiveness of scaffold-based therapy for osteochondral lesions of the talus (OLT).

METHODS

A systematic search of MEDLINE and EMBASE databases was performed during August 2016 and updated in January 2017. Included studies were evaluated with regard to the level of evidence (LOE) and quality of evidence (QOE) using the Modified Coleman Methodology Score. Variable reporting outcome data, clinical outcomes, and the percentage of patients who returned to sport at previous level were also evaluated.

RESULTS

Twenty-eight studies for a total of 897 ankles were included; 96% were either LOE III or IV. Studies were designated as either of poor or fair quality. There were 30 treatment groups reporting six different scaffold repair techniques: 13 matrix-induced autologous chondrocyte transplantation (MACT), nine bone marrow derived cell transplantation (BMDCT), four autologous matrix-induced chondrogenesis (AMIC), and four studies of other techniques. The categories of general demographics (93%) and patient-reported outcome data (85%) were well reported. Study design (73%), imaging data (73%), clinical variables (49%), and patient history (30%) were also included. The weighted mean American Orthopaedic Foot and Ankle Society (AOFAS) score at final follow-up was: 86.7 in MACT, 88.2 in BMDCT, and 82.3 in AMIC. Eight studies reported that a weighted mean of 68.3% of

patients returned to a previous level of sport activity.

CONCLUSION

Scaffold-based therapy for OLT may produce favorable clinical outcomes, but low LOE, poor QOE, and variability of the data have confounded the effectiveness of this treatment.

Key words: Scaffold; Ankle; Talar osteochondral lesion; Systematic review; Cartilage

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Core tip: This systematic review demonstrated that scaffold-based therapy for lesions of the talus (OLT) may produce favorable clinical outcomes. However, 96% of included studies were classified into the category of poor level of evidence and no papers were of good methodological quality. Therefore, careful attention should be paid when evaluating scaffold-based therapy for OLT. In addition, large variability and underreporting of clinical data between studies made it difficult to reliably compare the results. Further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy for OLT, especially when compared to the available traditional treatments.

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INTRODUCTION

Numerous surgical treatment strategies for osteochondral lesions of the talus (OLT) have been proposed, but a universally ideal treatment has yet to be established^[1,2]. The operative treatment for OLT can be divided into two broad categories: Reparative and replacement procedures. Reparative procedures aim to regenerate tissue with biomechanical properties similar to normal hyaline cartilage. Bone marrow stimulation (BMS) is the most common reparative procedure, which stimulates mesenchymal stem cell proliferation and promotes fibrous cartilage repair tissue at the defect site. However, the fibrous cartilage repair tissue has different biological and mechanical properties compared to native hyaline cartilage and is likely to degenerate over time^[3]. Autologous chondrocyte implantation (ACI) is another reparative procedure that attempts to regenerate damaged cartilage with more hyaline-like repair tissue, but this procedure has the disadvantage of the need for a two-staged intervention, which increases both cost and the potential for morbidity^[4].

Recently, tissue-engineering approaches using various

types of bioavailable scaffolds has emerged with greater potential for cellular differentiation and maturation. The templates are typically seeded with elements selected to improve the quality of reparative cartilage and include stem cells and growth factors. Matrix-induced autologous chondrocyte transplantation (MACT) is a second-generation ACI technique, which uses a type I / III bilayer collagen membrane seeded with cultured autologous chondrocytes. However, MACT also requires a two stage procedure^[5,6]. Autologous matrix-induced chondrogenesis (AMIC) is a one-step scaffold-based therapy that combines bone marrow stimulation (BMS) with the use of a porcine collagen I / III matrix scaffold^[7]. Bone marrow-derived cell transplantation (BMDCT) is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material^[8].

Scaffold-based therapy for OLT offers alternative reparative procedures and is quickly becoming more popular as data supporting clinical efficacy increases^[9]. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy on OLT to date.

The purpose of the current systematic review was to clarify the effectiveness of scaffold-based therapy for OLT based on available clinical evidence.

MATERIALS AND METHODS

Search strategy

Two independent reviewers performed a systematic review of the databases PubMed/MEDLINE and EMBASE in January 2017 based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[10].

The combination of search terms were: (cartilage OR cartilage injury OR cartilage damage OR cartilage repair OR cartilage defect OR osteochondral lesion OR osteochondral dissecans OR osteochondral defect OR osteochondral injury OR osteochondral fracture OR osteochondritis dissecans) AND (ankle OR talus OR tibia OR talocrural joint) AND (scaffold OR scaffold-based repair OR matrix-assisted chondrocyte implantation OR cartilage regeneration OR osteochondral repair). The reference list of all articles and relevant studies were also scanned for additional articles potentially not identified through our electronic search alone.

The inclusion and exclusion criteria are shown in the Table 1. No time limit was given to publication date.

The titles and abstracts were reviewed by applying the aforementioned criteria, and the full text of potentially relevant studies was then selected. Scaffold-based therapy for OLT was defined as operative treatment using any scaffolds for OLT.

Differences between reviewers were discussed until agreement was achieved, and the senior author was consulted in the event of persistent disagreement.

Assessment of level of evidence

Two independent investigators reviewed each study and the LOE was determined using previously published

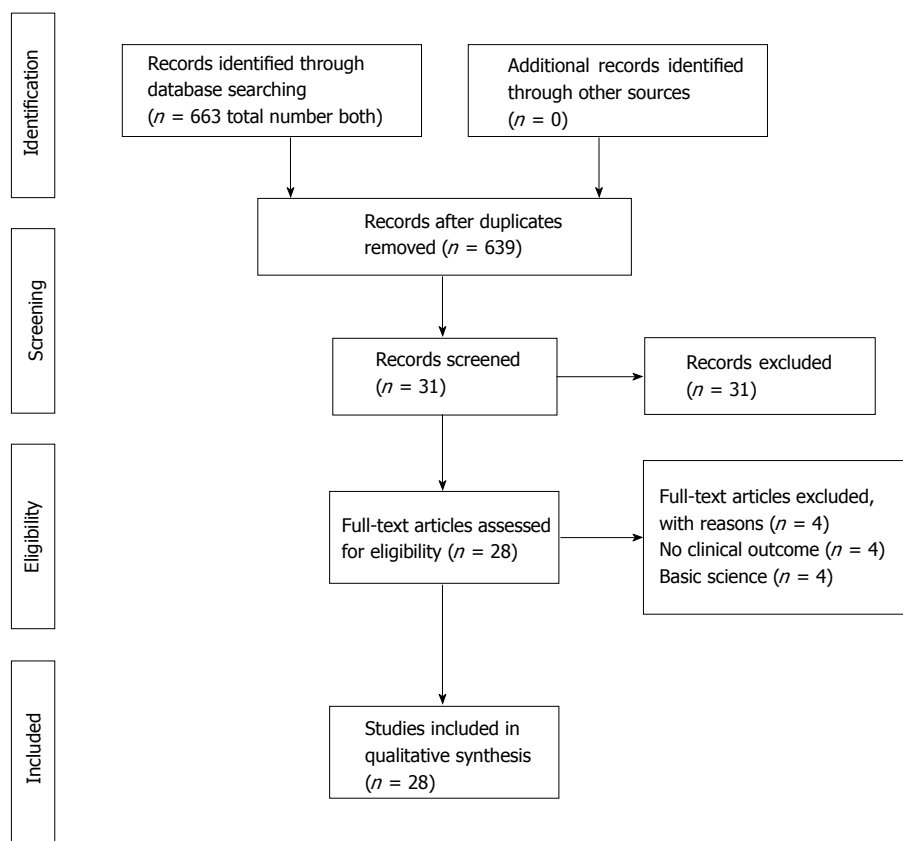


Figure 1 PRISMA flowchart outlining the systematic review.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> Therapeutic clinical studies evaluating the effect of scaffolds for ankle cartilage repair All patients included had > 6-mo follow-up Published in a peer-reviewed journal Published in English Full-text version available
Exclusion criteria	<ul style="list-style-type: none"> Review articles Case reports Technique articles Cadaveric studies Animal studies <i>In vivo</i> studies

criteria^[11].

Assessment of methodological quality of evidence

Two independent investigators evaluated the methodological quality of evidence (QOE) of the included studies using the Modified Coleman Methodology Score (MCMS) (Table 2)^[12,13]. Instances of discrepancy were resolved by consensus and if any disagreement persisted, a senior author was consulted and a consensus was reached. Excellent studies were considered those that scored 85 to 100 points; good studies scored 70 to 84 points; fair studies scored 55 to 69 points, and poor studies scored less than 55 points^[14].

Data extraction and analysis

Two reviewers independently extracted data from each study and assessed variable reporting of outcome data using parameters of previously published criteria^[15]. In addition, clinical outcomes and the percentage of patients who returned to sport at previous level were evaluated.

Statistical analysis

All statistical analysis was performed using a commercially available statistical software package (SAS 9.3; SAS Institute, Inc., Cary, NC, United States). Descriptive statistics were calculated for each study and parameters analyzed. For each variable, the number and percentage of studies that reported the variable was calculated. Variables were reported as weighted average ± weighted standard deviation where applicable.

RESULTS

After full text review, 28 clinical studies for a total of 897 ankles were identified for inclusion in the current study (Figure 1)^[4-8,16-38]. The weighted mean follow-up was 37.7 (range 6-87) mo, with only three studies reporting a follow-up time of greater than five years^[20,22,24].

Of the 28 clinical studies, there were 30 treatment groups, including six different scaffold-based therapies: 13 MACT^[5,6,16-26], nine BMDCT^[4,8,26-31], four AMIC^[7,32-34], two cartilage extracellular matrix^[35,36], one autologous

Table 2 Modified Coleman Methodology Score

		Score
Part A: Only 1 score to be given for each section		
Number of study patients	> 60	10
	41-60	7
	20-40	4
	< 20, not stated	0
Mean follow-up (mo)	> 24	5
	12-24	2
	< 12, not stated or unclear	0
Number of different surgical procedures included in each reported outcome	1	10
	> 1, but > 90% of patients undergoing the 1 procedure	7
	Not stated, unclear, or < 90% of subjects undergoing the 1 procedure	0
Type of study	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
Diagnostic certainty (MRI)	In all	5
	In > 80%	3
	In < 80%	0
Description of surgical procedure given	Adequate (technique stated and necessary details of that type of procedure provided)	5
	Fair (technique only stated without elaboration)	3
	Inadequate, not stated, or unclear	0
Description of postoperative rehabilitation	Well described (ROM, WB, and sport)	10
	Not adequately described (2 items between ROM, WB, and sport)	5
	Protocol not reported	0
Part B: Scores may be given for each option in each of the 3 sections if applicable		
Outcome criteria	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (<i>e.g.</i> , at best outcome after surgery or follow-up)	2
	Objective, subjective, and imaging criteria	6
	2 items between objective, subjective, and imaging criteria	4
	Objective, subjective, or radiological criteria	2
Procedure for assessing outcomes	Patients recruited (results not taken from surgeons' files)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by patients themselves with minimal investigator assistance	3
Description of patient selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported	
	> 80%	5
	< 80%	3
	Eligible patients not included in study satisfactorily accounted for or 100% recruitment	5

collagen-induced chondrogenesis (ACIC)^[37], and one cell free scaffold therapy^[38]. All included studies of scaffold-based therapy were summarized in Table 3. Patient demographics and clinical characteristics of each procedure are shown in Table 4.

LOE

There was one (3.6%) study of LOE II^[30], three studies (10.7%) of LOE III^[4,24,26], and 24 studies (85.7%) of LOE

IV^[5-8,16-23,25,27-29,31-38] (Table 5) according to established criteria^[11]. No study of LOE I was reported. The further data of LOE in each procedure group was shown in Table 5.

QOE

The weighted mean MCMS of the overall population of studies was 49.3 ± 10.0 out of a possible 100 points. There were seven studies (25%) of fair

Table 3 Studies of two-step and one-step procedures for ankle scaffold-based repair

Procedure	Product	Scientific publication	Type of study	LOE	No. of patients	Lesion size (cm ²)	Follow-up (mo)	Results
Two-step MACT	MACI	Schneider <i>et al</i> ^[6] , 2009	Case series	IV	20	2.3	21	Significant improvement in functional score Pain improved in 70% of patients
		Giza <i>et al</i> ^[5] , 2010	Case series	IV	10	1.3	24	Significant clinical improvement at 1 yr and maintained at 2 yr
		Aurich <i>et al</i> ^[16] , 2011	Case series	IV	18	-	25	Significant improvement in all clinical scores 64% were excellent or good Age and symptoms duration were correlated with results
		Dixon <i>et al</i> ^[17] , 2011	Case series	IV	25	1.3	44	72% improved symptoms 78% patients over 40 yr reported restricted recreational activity
		Lee <i>et al</i> ^[18] , 2013	Case series	IV	38	1.9	24	Functional outcomes improved significantly at 2 yr 68% were excellent or good outcome 75% ICRS grade I or II in 2 nd look arthroscopy at 1 yr
	Hyalograft C	Johnson <i>et al</i> ^[19] , 2013	Case series	IV	18	1.9	82	Functional outcomes improved at final follow-up
		Giannini <i>et al</i> ^[20] , 2014	Case series	IV	46	1.6	87	Significant clinical improvement at 1 yr and maintained at 3 yr; 3 failures
		Giannini <i>et al</i> ^[21] , 2008	Case series	IV	46	1.6	36	Significant clinical improvement at 1 yr and 3 yr Results correlated with age and previous surgery Hyaline-like cartilage regeneration in histological evaluation
		Battaglia <i>et al</i> ^[22] , 2011	Case series	IV	20	2.7	60	Significant clinical improvement T2 mapping MRI showed 69% of lesion are covered with repair tissue
		Nehrer <i>et al</i> ^[23] , 2011	Case series	IV	13	-	47	Significant clinical improvement in all cases
Two-step BMDCT	Spontostan Powder HYAFF-11	Domayer <i>et al</i> ^[24] , 2012	Comparative study	III	18	1.2	65	Significant clinical improvement but no significant difference compared to MFX group No difference between MFX and MACT on T2 maps
		Apprich <i>et al</i> ^[25] , 2012	Case series	IV	10	1.2	48	Significant clinical improvement No differences in functional outcome and MOCART score between MFX and MACT
	Spontostan Powder HYAFF-11	Giannini <i>et al</i> ^[8] , 2009	Case series	IV	48 (25 HA membrane, 23 collagen powder)	2.1	29	Significant clinical improvement at 1 yr maintained at 2 yr Similar results with two scaffolds Correlation between clinical outcome and lesion size
		Giannini <i>et al</i> ^[26] , 2010	Comparative study	III	25 BMDCT 46 two-step MACT	2.2 1.6	39 57	Significant clinical improvement at 1 yr and further improvement at 3 yr 76% complete intergration with surrounding cartilage on MRI Hyaline-like cartilage tissue on histological evaluation
		Battaglia <i>et al</i> ^[27] , 2011	Case series	IV	20	1.5	24	85% excellent or good clinical results at 2 yr 78% of lesion are covered with repair tissue comparable to hyaline cartilage
Spontostan Powder HYAFF-11	Giannini <i>et al</i> ^[28] , 2013	Case series	IV	49	2.1	29	Significant clinical improvement at 1 yr with subsequent significant decrease at 2 and 3 yr 78% of repaired tissue similar to hyaline cartilage on T2 maps	
Spongostan Powder	Buda <i>et al</i> ^[29] , 2014	Case series	IV	64	5.3	53	Clinical results peaked at 2 yr, declining gradually at follow-up of 6 yr	

	Biopad	Cadossi <i>et al</i> ^[30] , 2014	Comparative study	III	15 BMDCT 15 BMDCT with PEMF	2 1.9	12 12	Significant clinical improvement in both groups
	HYAFF-11	Buda <i>et al</i> ^[4] , 2015	Case series	IV	40	1.8	48	Significant clinical improvement Higher presence of hyaline-like cartilage in BMDCT than ACI on MRI T2 mapping
	HYAFF-11 Spongostan Powder	Vannini <i>et al</i> ^[31] , 2017	Case series	IV	140	2	26	Significant clinical improvement at 2 yr maintained at 4 yr Return to sports at preinjury level; 32.1% at 12 mo, 72.8% at 48 mo
AMIC	Unclear	Wiewiorski <i>et al</i> ^[7] , 2013	Case series	IV	23	-	23	Significant clinical improvement
	Chondro-Gide	Valderrabano <i>et al</i> ^[32] , 2013	Case series	IV	26	-	31	Significant clinical improvement Normal signal intensity of repair tissue was seen in 15% on MRI
	Chondro-Gide	Kubosch <i>et al</i> ^[33] , 2016	Case series	IV	17	2.4	39	Significant clinical improvement MOCART score correlated with AOFAS score
	Chondro-Gide	Wiewiorski <i>et al</i> ^[34] , 2016	Case series	IV	60	-	47	Calcaneal osteotomy was performed in 63% of patients Low rate for return to sports; postoperative sports activity levels remain stable when compared with preoperative levels
Cartilage ECM	BioCartilage	Desai S ^[35] , 2016	Case series	IV	9	1.3	12	78% excellent, 22% good clinical outcomes
		Clanton <i>et al</i> ^[36] , 2014	Case series	IV	7	-	8	Significant clinical improvement
ACIC	Cartifill	Volpi P <i>et al</i> ^[37] , 2014	Case series	IV	5	3.1	6	Significant clinical improvement at 6 mo
Cell-free scaffold	MaioRegen [®]	Christensen <i>et al</i> ^[38] , 2015	Case series	IV	4	-	30	No clinical scores improvement No improvement in MOCART score and 3 patients had 0%-10% bone formation in defect at 1 yr on CT

Table 4 Patient demographics and clinical characteristics

	Procedure						
	Total	MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Treatment groups, <i>n</i>	30	13	9	4	2	1	1
Ankles, <i>n</i>	897	330	416	126	16	5	4
Sex, male/female/unknown, <i>n</i>	501/322/72	174/111/45	238/153/22	79/47/0	7/9/0	3/2/0	-
Age, yr, weighted mean (range)	30.9 (19-61)	30.1	30.2	34.9	42.7	25.6	-
Duration of symptoms, mo, weighted mean (range)	34.3 (6-216)	34.5	36.5	23	-	-	-
Lesion size, mm ² , weighted mean (range)	215 (116-527)	171	248	240	130	-	-
Follow-up, mo, weighted mean (range)	37.7 (6-87)	45.8	32.7	38.2	10.4	6	30

Table 5 Level and quality of evidence of included studies *n* (%)

Level of evidence	Total Studies	Procedure groups					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
1	0	0	0	0	0	0	0
2	1 (3.6)	0	2 (22.2)	0	0	0	0
3	3 (10.7)	2 (15.4)	2 (22.2)	0	0	0	0
4	24 (85.7)	11 (84.6)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)
Quality of evidence							
Excellent (MCMS ≥ 85)	0	0	0	0	0	0	0
Good (MCMS 70-84)	0	0	0	0	0	0	0
Fair (MCMS 55-69)	7 (25.0)	3 (23.1)	4 (44.4)	0	0	0	0
Poor (MCMS < 55)	21 (75.0)	10 (76.9)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)

quality^[8,18,20,21,30,31,38] and the remainder (75%) were of poor quality^[4-7,16,17,19,22-29,32-37] (Table 5). Further QOE

Table 6 Data reported (in percentage)

	Total	Procedure					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Procedure groups, <i>n</i>	30	13	9	4	2	1	1
Demographic information	93	92	94	100	100	100	0
Sex	90	85	89	100	100	100	0
Mean age + range	97	100	100	100	100	100	0
Patient history	30	35	31	44	13	0	0
Body mass index	33	31	33	50	50	0	0
Mean duration of symptoms	23	38	22	25	0	0	0
Previous traumatic experience(s)	33	38	44	50	0	0	0
Activities of daily living/athletic participation	30	31	22	50	0	0	0
Study design	73	71	78	72	56	63	38
Type of study	50	23	56	25	0	0	100
Number of patients	97	100	100	100	100	100	0
Percentage of patients in follow-up	97	100	100	100	100	100	0
Consecutive patients	23	23	22	50	0	0	0
Follow-up time + range/standard deviation	100	100	100	100	100	100	100
Method of lesion size measurement	43	54	44	50	0	0	0
Lesion classification system utilized	77	77	100	50	50	100	0
Surgical approach used to access lesion	97	92	100	100	100	100	100
Clinical variables	49	53	50	58	33	33	33
Lesion size	93	100	100	75	50	100	100
Lesion location	77	77	100	75	50	0	0
Presence of cyst	13	23	0	25	50	0	0
Associated pathology	13	23	0	25	0	0	0
Concomitant procedures	20	15	22	50	0	0	0
Description of rehabilitation	80	77	78	100	50	100	100
Imaging data	73	81	83	75	50	0	100
Imaging used to identify lesion	80	92	89	75	50	0	100
Imaging used at follow-up	67	69	78	75	50	0	100
Patient-reported outcomes	85	85	100	88	0	100	100
Pain, function, and activity scale, pre-operative	80	77	100	75	0	100	100
Pain, function, and activity scale, at follow-up	90	92	100	100	0	100	100

data is shown in Table 5.

Variable reporting of outcome data

The defined data that were reported in the studies included in this review are listed and the each data according to procedure group is shown in Table 6. General demographic information including age and gender were reported in 93% of the studies. While the study design, imaging data, and patient-reported outcomes were well-reported variables with 73%, 73% and 85% respectively, patient history was the least reported variable of all with 30% of the data being reported. Clinical variables were reported in only 49% of studies.

Clinical outcomes were evaluated using a number of different scoring systems for scaffolds-based therapy for OLT (Table 7). The American Orthopaedic Foot and Ankle Society (AOFAS) score was the most frequently utilized in 25 studies of the included [4-8,16-18,20-34,37,38]. Of the 25 studies that used AOFAS, 22 studies investigated both pre- and post-operative scores [4-8,16,18,20-23,25-32,34,37,38].

Twelve of 13 MACT groups reported pre and post-operative AOFAS scores and of the 310 patients who underwent MACT [5,6,16-18,20-26], the mean AOFAS score improved from 59.1 to 86.7 at a mean follow-up of 47.9 mo. Of the 416 patients from the nine BMDCT groups [4,8,26-31], the mean AOFAS score improved from

61.1 to 88.2 at a mean of 32.7 mo of follow-up. Of the 126 patients from the four AMIC groups [7,32-34], the mean AOFAS score improved from 50.7 to 82.3 at a mean follow-up of 38.2 mo. Of the two cartilage ECM studies included, one publication reported outcomes at less than one year follow-up [36], and the other one did not describe clinical outcomes [35]. There was only one publication reporting ACIC data but clinical evaluation was insufficient due to a follow-up of only six mo [37]. In the cell-free scaffold group, only one study was published, which showed no clinical improvement in AOFAS score at a mean 30 mo (from 48.7 to 52.7) follow-up. However, these results only included four studies [38].

In this systematic review, 12 procedure groups reported sequential clinical outcomes at two or more post-operative time points [4,5,8,18,20,21,26,28-31]. Four groups, which were all BMDCT studies, found temporal improvement in AOFAS scores over the first 2-3 years of post-operative follow-up with a mean decrease in AOFAS score of 87.1 reported at a mean 41.8 mo follow-up [4,28,29,31]. In contrast, eight groups, including four MACT and four BMDCT groups, demonstrated that there were no deteriorations during a weighted mean 38-mo follow-up [5,8,18,20,21,26,30].

Return to sport activity at previous level

Overall, eight studies (MACT: One study, AMIC: Two

Table 7 Clinical outcome scores utilized in included studies *n* (%)

Score	Studies, total	Procedure group					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
AOFAS	25 (89)	12 (92)	9 (100)	4 (100)	0 (0)	1 (100)	1 (100)
VAS	7 (25)	1 (8)	2 (22)	4 (100)	0 (0)	1 (100)	0 (0)
Tegner activity score	3 (11)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	1 (100)
SF-36	2 (7)	1 (8)	2 (22)	0 (0)	0 (0)	0 (0)	0 (0)
FFI	2 (7)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
FADI	1 (4)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)
HSS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEAS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AHS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AAOS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ARS	1 (4)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
Halasi score	1 (4)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Mazur ankle score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cincinnati score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AAOS: American Academy of Orthopaedic Surgeons; AHS: Ankle-Hindfoot Score; AOFAS: American Orthopaedic Foot and Ankle Society; ARS: Activity Rating Scale; FADI: Foot and Ankle Disability Index; FFI: Foot Function Index; HSS: Hannover Scoring System; LEAS: University of California Lower Extremity Activity Scale; SF-36: Short Form-36 Health Survey; VAS: Visual analog scale.

studies, BMDCT: five studies) reported that a mean 68.3% of patients receiving scaffold-based therapy with mean lesion size of 250 mm² returned to previous sport activity at previous level^[4,8,21,28,29,31,32,34]. Of the MACT procedures, Giannini *et al.*^[21] showed that 20 of 29 patients (69%) returned to sport at previous levels. In patients treated with AMIC procedures, Valderrabano *et al.*^[32] reported only nine of 20 patients (45%) returned to previous sport activity level, and Wiewiorski *et al.*^[34] also showed no significant difference when comparing preoperative and postoperative activity scores (ARS, Tegner). BMDCT was the most reported in five studies, and of these studies, 74.5% of patients were able to resume sports at preinjury level, with a range of 69% to 78%^[4,8,28,29,31].

DISCUSSION

The results from this systematic review demonstrate that recommendations for scaffold-based therapy based solely on evidence is not yet conclusive. In the current evaluation, 96% of included studies in which scaffold-based therapy was performed for the treatment of OLT were classified into the category of poor LOE. In addition, of 28 included articles, no papers were of good or better methodological quality. According to the principles of evidence-based medicine^[39], a high level of clinical evidence and good methodological quality are fundamentally warranted to treat patients because low LOE and QOE studies are more likely to show overestimated outcomes compared to higher LOE and QOE studies^[40,41]. Careful attention therefore should be paid when evaluating outcomes following the studies of scaffold-based therapy for OLT.

The results from the current systematic review demonstrate large variability and underreporting of clinical data between studies reflecting and inability to compare the

results across studies. These inconsistencies and general underreporting of data make it difficult to pool data, which furthermore makes it difficult to draw conclusions about effectiveness of the use of scaffold in the treatment for OLT. As Hannon *et al.*^[15] described, adequate reporting of data in the studies of the treatment for OLT should be required to perform high quality studies, and investigators should be encouraged to implement data collection both before and after surgery according to recommended list described by Hannon *et al.*^[15] in this review, the categories of imaging data were reported in 73% of included studies. Compared with reporting of outcome data on microfracture for OLT in the systematic review by Hannon *et al.*^[15], imaging data was reported in only 39% among the studies. However, this review showed a higher percentage of reporting of imaging data (73%). Nevertheless, only 67% of studies used MRI for patient follow-up evaluation, although MRI evaluation for scaffold-based treatment of OLT is crucial because the aim of the use of scaffolds and is generally believed to promote the subchondral bone and cartilage repair. In addition, the categories of clinical variables and patient history were reported only with 49% and 30% respectively. As these data including BMI, lesion location, presence of cyst, associated pathology, and concomitant procedures can have significant effect on patient outcome, what is alarming is that appropriate information is not enough taken in the current studies.

Lesion size has been widely accepted as the most commonly used predictor of clinical outcomes after BMS for OLT^[42,43]. Choi *et al.*^[42] demonstrated that BMS should be indicated for lesions less than 150 mm² and lesions greater than this value resulted in poor outcomes. More recently, Ramponi *et al.*^[13] suggested that BMS could be best reserved for lesion size of less than 107.4 mm² rather than 150 mm². In the current review, however, the mean lesion size treated with scaffolds was 215 mm², which is much larger than traditional indication

size for BMS or the most current new indication size of 107 mm²^[13]. This suggests that the use of scaffolds may further improve the potential of reparative techniques. However, further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy on OLT because of low LOE and QOE and the large variability in the data.

Despite of high frequency of OLT in the athletic population, little is reported regarding return to sport following surgical treatment of OLT in this population. In the current review, weighted mean 68.3% of patients receiving scaffold therapy with weighted mean 250 mm² of lesion size returned to previous sport activity at previous level in eight studies. There are no studies investigating the effectiveness of BMS alone for athletic populations who have large lesion as described above, but Choi *et al.*^[42] reported clinical failure rate in patients with lesion area ≥ 150 mm² was 80%. Furthermore, Chuckpaiwong *et al.*^[43] reported a 97% of failure rate in 32 patients with a lesion area ≥ 150 mm². This suggests that the use of scaffolds may provide better outcomes than BMS alone for larger lesions but high quality studies are warranted. On the other hand, in replacement procedures, including autologous osteochondral transplantation, which is generally indicated for larger lesions, several studies reported that more than 90% of patients returned to play sport at previous levels^[44,45]. Although there is inconsistency in indications for the treatment strategy, the rate of return to sport following scaffold-based therapy appears to be relatively lower than AOT procedures. The highest rate of return to sport after scaffold-based therapy was only 78.0% in athletes treated with BMDCT^[31]. However, there was variability of sport type, postoperative rehabilitation protocol, and time to return to sport, which makes it difficult to assess these results appropriately.

Our review found that there were 12 different scoring systems used to assess clinical outcomes, with AOFAS score being the most commonly used (89%). However, there remains no validated scoring system for the clinical follow-up for the treatment of OLT^[13]. Moreover, four BMDCT groups have shown that clinical outcomes deteriorate after peaking at 2-3 year post-operatively^[4,28,29,31], whereas four MACT and four BMDCT groups have no deterioration during follow-up^[5,8,18,20,21,26,30]. A potential reason for these lags in clinical outcome data may be the invalid clinical evaluation methods after OLT surgery in addition to the use of the different kinds of scaffolds. A novel validated scoring system for the clinical follow-up of the treatment for OLT are currently warranted.

The appropriate treatment for OLT is still controversial. While the ideal procedure would regenerate a tissue with biomechanical properties similar to normal hyaline cartilage, reparative techniques can offer the replacement of the articular cartilage with a hyaline-like repair tissue. Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as ACI, the first generation approach for cartilage treatment, has evident biological and surgical limitations^[46]. In fact, the use of scaffolds has overcome

the drawbacks and simplified the procedure. However, any available substitute materials have not yet matched the properties of the normal cartilage, and there is no consensus about the superior effectiveness of these procedures over the other procedures, including replacement procedures. While the scaffold-based treatment has shown promising clinical results in numerous studies of case series, the current systematic review showed low LOE and poor methodological quality of the use of scaffolds for OLT. Further long-term comparative studies are warranted to investigate the potential of a bioengineered approach compared to other treatments. Furthermore, the definitive indications for this technique, including lesion size and character of the lesion, still remains controversial^[13].

This systematic review has several inherent limitations and/or potential biases. The criterion was limited to MEDLINE, EMBASE and Cochrane Library Database articles published exclusively in English. The variables may not be all inclusive of data in each study, but they should be a representative summary of the most commonly used data. Another inherent concern was the overlapping of cohorts or subgroups of several cohorts studies in longitudinal follow-up studies. Finally, the data extraction was not performed blindly, but was performed by two independent reviewers and later confirmed by the lead author.

In conclusion, this systematic review demonstrated that the scaffold-based therapy for the treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT. Further, well-designed studies, are necessary to determine the effectiveness of the use of scaffold for the treatment of OLT, especially when compared to available traditional treatments.

COMMENTS

Background

Recently scaffold-based therapy for osteochondral lesions of the talus (OLT) has become more popular as an alternative reparative procedure. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy in the treatment of OLT to date. In this study, the effectiveness of scaffold-based therapy was systematically reviewed based on available clinical evidence.

Research frontiers

Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as autologous chondrocyte implantation (ACI), the first generation approach for cartilage treatment, has evident biological and surgical limitations. Recently, the use of scaffolds has overcome the drawbacks and simplified the procedure.

Innovations and breakthroughs

The scaffold-based treatment has shown promising clinical results in numerous studies of case series and the use of scaffolds may further improve the potential of reparative techniques. Retrieved manuscripts were reviewed by the authors, and the data were extracted.

Applications

This systematic review suggests that the scaffold-based therapy for the

treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT.

Terminology

Matrix-induced autologous chondrocyte transplantation is a second-generation ACI technique, which uses a type I/III bilayer collagen membrane seeded with cultured autologous chondrocytes. Autologous matrix-induced chondrogenesis is a one-step scaffold-based therapy that combines bone marrow stimulation with the use of a porcine collagen I/III matrix scaffold. Bone marrow-derived cell transplantation is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material.

Peer-review

The paper adequately concludes what is already suspected in that variable quality, small studies with limited outcome data serve to confuse the authors' knowledge. It's a useful review.

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