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

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Objective: 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.

Conclusion: Team cooperation is essential to achieve optimal clinical outcomes in the treatment of osteochondral lesions of the talus.
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 repair OR osteochondral injury OR osteochondral fracture OR osteochondral dissecans OR osteochondral defect OR osteochondral dissecans) AND (ankle OR talus OR tibia OR talocentral 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

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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) \cite{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 \cite{14}.

Table 1  Inclusion and exclusion criteria

| Inclusion criteria                                                                 |
|------------------------------------------------------------------------------------|
| 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                                                                |
|------------------------------------------------------------------------------------|
| Review articles                                                                   |
| Case reports                                                                       |
| Technique articles                                                                |
| Cadaveric studies                                                                  |
| Animal studies                                                                     |
| In vivo studies                                                                    |

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 \cite{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) \cite{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 \cite{20,22,24}.

Of the 28 clinical studies, there were 30 treatment groups, including six different scaffold-based therapies: 13 MACT \cite{5,6,16-26}, nine BMDCT \cite{4,8,26-31}, four AMIC \cite{7,32-34}, two cartilage extracellular matrix \cite{35,36}, one autologous....
collagen-induced chondrogenesis (ACIC)\textsuperscript{[37]}, and one cell free scaffold therapy\textsuperscript{[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\textsuperscript{[30]}, three studies (10.7%) of LOE III\textsuperscript{[4,24,26]}, and 24 studies (85.7%) of LOE IV\textsuperscript{[5-8,16-23,25,27-29,31-38]} (Table 5) according to established criteria\textsuperscript{[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 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 (e.g., 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 | 5 |
| > 80% | 5 |
| < 80% | 3 |
| Eligible patients not included in study satisfactorily accounted for or 100% recruitment | 5 |
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 (cm²) | Follow-up (mo) | Results |
|-----------|---------|------------------------|---------------|-----|----------------|-----------------|---------------|---------|
| Two-step MACT | MACI | Schneider et al[6], 2009 | Case series | IV | 20 | 2.3 | 21 | Significant improvement in functional score |
| | | Giza et al[5], 2010 | Case series | IV | 10 | 1.3 | 24 | Significant clinical improvement at 1 yr and maintained at 2 yr |
| | | Aurich et al[16], 2011 | Case series | IV | 18 | - | 25 | Significant improvement in all clinical scores |
| | | Dixon et al[13], 2011 | Case series | IV | 25 | 1.3 | 44 | Pain improved in 70% of patients |
| | | Lee et al[14], 2013 | Case series | IV | 38 | 1.9 | 24 | Significant clinical improvement at 1 yr and maintained at 2 yr |
| | | Johnson et al[15], 2013 | Case series | IV | 18 | 1.9 | 82 | Significant clinical improvement at 1 yr and maintained at 3 yr; 3 failures |
| | | Giannini et al[17], 2008 | Case series | IV | 46 | 1.6 | 36 | Results correlated with age and previous surgery |
| Hyalograft C | | Battaglia et al[18], 2011 | Case series | IV | 20 | 2.7 | 60 | Hyaline-like cartilage regeneration in histological evaluation |
| | | Nehrer et al[19], 2011 | Case series | IV | 13 | - | 47 | Significant clinical improvement at final follow-up |
| | | Domayer et al[20], 2012 | Comparative study | III | 18 | 1.2 | 65 | Significant clinical improvement but no significant difference compared to MFX group |
| | | Apprich et al[21], 2012 | Case series | IV | 10 | 1.2 | 48 | No difference between MFX and MACT on T2 maps |
| | | Spontostan Powder HYAFF-11 | Giannini et al[22], 2009 | Case series | IV | 48 (25 HA membrane, 23 collagen powder) | 2.1 | 29 | Significant clinical improvement at 1 yr maintained at 2 yr |
| | | Spontostan Powder HYAFF-11 | Giannini et al[23], 2010 | Comparative study | III | 25 BMDCT 46 two-step MACI | 2.2 | 39 | Similar results with two scaffolds |
| | | HYAFF-11 | Battaglia et al[24], 2011 | Case series | IV | 20 | 1.5 | 24 | Correlation between clinical outcome and lesion size |
| | | Spontostan Powder HYAFF-11 | Giannini et al[25], 2013 | Case series | IV | 49 | 2.1 | 29 | Significant clinical improvement at 1 yr and further improvement at 3 yr |
| | | Spongostan Powder | Buda et al[26], 2014 | Case series | IV | 64 | 5.3 | 53 | Significant clinical improvement at 1 yr and following intervention with surrounding cartilage on MRI |

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and the remainder (75%) were of poor quality and the remainder (75%) were of poor quality. Further QOE
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\(^{[4,8,16,18,20-21,25-22,34,37,38]}\).

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\(^{[7,28-30]}\), 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\(^{[30]}\), 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\(^{[39]}\).

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\(^{[4,26,29,31]}\). 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

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Table 6  Data reported (in percentage)

| Procedure                        | Total     | MACT      | BMDCT     | AMIC      | Cartilage ECM | ACIC      | Cell-free scaffold |
|----------------------------------|-----------|-----------|-----------|-----------|---------------|-----------|--------------------|
| Procedure groups, n              | 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       | 0                  |
| 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       | 0                  |
| 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                |
of the current 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[45] 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 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[43] 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 of scaffold-based therapy for OLT. In addition, the categories 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 scores 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[45] 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 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.

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| 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) | 0 (0) |
| 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) |
| AACS | 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.
size for BMS or the most current new indication size of 107 mm$^2$\textsuperscript{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 mm$^2$ of lesion size returned to prior 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.\textsuperscript{42} reported clinical failure rate in patients with lesion area $\geq 150$ mm$^2$ was 80%. Furthermore, Chuckpaiwong et al.\textsuperscript{43} reported a 97% of failure rate in 32 patients with a lesion area $\geq 150$ mm$^2$. 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 level\textsuperscript{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\textsuperscript{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\textsuperscript{13}. Moreover, four BMDCT groups have shown that clinical outcomes deteriorate after peaking at 2-3 year post-operatively\textsuperscript{4,28,29,31}, whereas four MACT and four BMDCT groups have no deterioration during follow-up\textsuperscript{13,8,18,20,21,26,30}. 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\textsuperscript{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\textsuperscript{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.
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