Invited Review

Matrix-induced autologous chondrocyte implantation (mACI) versus autologous matrix-induced chondrogenesis (AMIC) for chondral defects of the knee: a systematic review

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Abstract

Introduction: Chondral defects of the knee are common and their treatment is challenging.
Source of data: PubMed, Google scholar, Embase and Scopus databases.
Areas of agreement: Both autologous matrix-induced chondrogenesis (AMIC) and membrane-induced autologous chondrocyte implantation (mACI) have been used to manage chondral defects of the knee.
Areas of controversy: It is debated whether AMIC and mACI provide equivalent outcomes for the management of chondral defects in the knee at midterm follow-up. Despite the large number of clinical studies, the optimal treatment is still controversial.
Growing points: To investigate whether AMIC provide superior outcomes than mACI at midterm follow-up.
Areas timely for developing research: AMIC may provide better outcomes than mACI for chondral defects of the knee. Further studies are required to verify these results in a clinical setting.

**Key words:** Knee, chondral defect, mACI, AMIC

### Introduction

Hyaline cartilage tissue is alymphatic and hypocellular, with low metabolic activity and limited regenerative capabilities.\(^1\)\(^-\)\(^3\) The healing process of chondrocytes often does not result in *restitutio ad integrum*, and residual chondral defects or a fibrotic scar are frequent.\(^4\)\(^,\)\(^5\) Focal chondral defects of the knee are debilitating, leading to marked decline in quality of life and, in athletes, a high chance of retirement from sport.\(^5\)\(^,\)\(^6\) Conservative strategies are often not adequate to manage focal chondral defects of the knee.\(^5\)\(^,\)\(^9\) Thus, surgical management is often required.\(^10\)\(^,\)\(^11\) Several different surgical strategies have been proposed to manage focal chondral defects of the knee.\(^12\)\(^-\)\(^14\) After its introduction, membrane-induced autologous chondrocyte implantation (mACI) has been broadly performed.\(^11\)\(^,\)\(^15\)\(^,\)\(^16\) In 2005, Behrens\(^17\) first described an enhanced microfractures technique, which quickly evolved into the autologous matrix-induced chondrogenesis (AMIC) procedure. Given its simplicity, AMIC quickly gained the favour of surgeons and patients.\(^18\)

To the best of our knowledge, no previous study compared these two strategies in a clinical setting for chondral defect of the knee. AMIC was supposed to perform better than the mACI procedure; however, no consensus has been reached, and updated evidenced-based recommendations are required. Thus, a systematic review was conducted to investigate whether AMIC provides better outcomes than mACI for knee chondral defects at midterm follow-up. This study focused on patient-reported outcome measures (PROMs) and complication rates. We hypothesized that AMIC and mACI procedures provided equivalent clinical outcome.

### Method

**Search strategy**

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).\(^19\) The PICO algorithm was preliminarily stated:

- **P** (Problem): knee chondral defect;
- **I** (Intervention): chondral regeneration;
- **C** (Comparison): AMIC versus mACI;
- **O** (Outcomes): PROMs and complications.

**Data source and extraction**

The literature search was conducted by two authors (Filippo Migliorini1 and Jörg Eschweiler) separately in January 2022. The following databases were accessed: PubMed, Google scholar, Embase and Scopus. The following keywords were used in combination: chondral, cartilage, articular, damage, defect, injury, chondropathy, knee, pain, matrix-induced, autologous, chondrocyte, transplantation, implantation, mACI, AMIC, therapy, management, surgery, outcomes, hypertrophy, failure, revision, reoperation, recurrence. The same authors independently screened the resulting articles from the search. The full-text of the articles of interest was accessed. A cross-reference of the bibliographies was also performed. Disagreements between the two authors were solved by a third author (Nicola Maffulli).

**Eligibility criteria**

All the studies investigating the outcomes of AMIC and/or mACI for knee chondral defects were accessed. Given the authors language abilities, articles in English, Italian, French, Spanish and
German were eligible. Levels I to IV of evidence studies, according to the Oxford Centre of Evidence-Based Medicine, were suitable. Only studies investigating a minimum of five patients were included. Abstracts, reviews, letters, opinion, editorials and registries were excluded. Biomechanics, animals or in vitro studies were not considered. Only studies that used a cell-free bioresorbable membrane were considered. Studies augmenting AMIC or mACI with less committed cells (e.g. bone marrow concentrate, mesenchymal stem cells) or growth factors were not considered. Studies involving patients with kissing lesions were not included, nor were those involving patients with end-stage osteoarthritis. Only studies that clearly stated the duration of the follow-up were eligible. Only studies which reported quantitative data with regards to the outcomes of interest were included in this study.

Data extraction

Data extraction was conducted independently by two authors (Filippo Migliorini and Jörg Eschweiler). Generalities of the included studies (author and year, journal, study design) and patients demographic at baseline were collected (length of symptoms prior of treatment, number of procedures, mean body mass index (BMI) and age of the patients, length of the follow-up, gender, mean defect size). For each of the two techniques, the following data were retrieved: Visual Analogue Scale (VAS), Tegner Activity Scale, International Knee Documentation Committee (IKDC) and the Lysholm Knee Scoring Scale. Data regarding the following complications were also collected: rate of hypertrophy, failures, revision surgeries and total knee arthroplasty. The recurrence of symptomatic chondral defects which affect negatively the patient quality of life was considered as failure.

Methodological quality assessment

The methodological quality assessment was accomplished by two independent authors (Filippo Migliorini and Jörg Eschweiler). The risk of bias graph tool of the Review Manager Software (The Nordic Cochrane Collaboration, Copenhagen) was used. The following risks of bias were evaluated: selection, detection, attrition, reporting and other sources of bias.

Statistical analysis

The statistical analysis was performed with IBM SPSS Version 25. Continuous data were reported as mean difference (MD), while binary data were evaluated using the odd ratio (OR) effect measure. The confidence interval (CI) was set at 95% in all the comparisons. T-test and \( \chi^2 \) were evaluated for continuous and binary data, respectively, with \( P < 0.05 \) considered statistically significant.

Results

Search result

A total of 503 articles were initially obtained and 107 were excluded as they were duplicates. A further 349 articles were excluded because they did not match the inclusion criteria: not focused on mACI or AMIC (N = 225), not focusing on knee (N = 37), study design (N = 51), not reporting quantitative data under the outcomes of interest (N = 12), combined with other committed cells (N = 12), other (N = 8), language limitations (N = 3), not clearly stating the duration of the follow-up (N = 1). Finally, 47 articles were available for this study. The results of the literature search are shown in Figure 1.

Methodological quality assessment

As 27% (12 of 45) of the investigations were randomized clinical trials, and 20% (9 of 45) were retrospective studies, the risk of selection bias of random sequence generation was moderate. The overall risk of selection bias of allocation concealment was low. Given the overall lack of blinding, detection bias was moderate-high. The risk of attrition and reporting bias across all included studies was low, as was the risk of other bias. In conclusion, the risk of
bias was moderate, attesting to this study acceptable methodological assessment (Fig. 2).

**Patient demographics**

Data from 1667 procedures were retrieved; 36% (600 of 1667 patients) were women. The mean follow-up was 37.9 ± 21.7 months. The mean age of the patients was 34.7 ± 6.5, and the mean BMI 25.5 ± 1.6 kg/m². The mean defect size was 3.9 ± 1.2 cm². Generalities and demographics of the study are shown in Table 1.

Good comparability was found between the two groups at baseline (Table 2).

**Outcomes of interest**

The AMIC group demonstrated greater values of IKDC (MD 7.7; \( P = 0.03 \)) and Lysholm (MD 16.1; \( P = 0.02 \)) scores. Similarity was found concerning
the VAS ($P = 0.5$) and Tegner ($P = 0.2$) scores (Table 3).

**Complications**

The AMIC group demonstrated lower rate of failures (OR 0.2; $P = 0.04$). Similarity was found concerning the rate of hypertrophy ($P = 0.05$), knee arthroplasty ($P = 0.4$) and revision surgery ($P = 0.07$) (Table 4).

**Discussion**

According to the main findings of the present systematic review, AMIC performed better than mACI for chondral defects of the knee at ~40 months follow-up. The rate of complications was noticeably lower in the AMIC group. While the Tegner and VAS scores were similar, the mean difference of the Lysholm and IKDC scales exceeded the minimally clinically important difference (MCID) in favour of the AMIC group.\(^{21,24}\)

mACI has been largely performed in patients with focal chondral defects of the knee.\(^{25,26}\) For the mACI procedure, an arthroscopy of the knee is performed first to assess cartilage status, identify the chondral defect and harvest chondrocytes from a non-weightbearing zone of the distal femur.\(^{27-29}\) Autologous chondrocytes are subsequently extracted and cultivated, and expanded in vitro for ~3 weeks, over a membrane that acts as medium for cell proliferation.\(^{30,31}\) In a second-step surgery, the defect is debrided and the membrane is secured into the defect.\(^{32,33}\) The current literature presents several clinical trials reporting the surgical outcomes of mACI. However, there are still controversies. The optimal surgical approach, whether arthrotomy, mini-arthrotomy or arthroscopy, has not been clarified. Additionally, there are several different membranes used for expansion (resorbable cell-free or cell-based, synthetic), and the most appropriate type of fixation (suture or fibrin glue) is still unclear.\(^{34-39}\)

Recently, AMIC has gained increasing interest.\(^{36,40-43}\) Differently from mACI, which uses laboratory expanded autologous chondrocytes, AMIC is a single session procedure which exploits the regenerative potential of bone marrow derived mesenchymal stem cells (BM-MSCs).\(^{14,44}\) After defect debridement and curettage, microfractures are performed.\(^{45,46}\) A membrane is then placed into the defect. BM-MSCs from the subchondral layer migrate into the membrane and regenerate the hyaline cartilage layer.\(^{12,37,48}\) Similar to mACI, AMIC can be performed through arthrotomy, mini-arthrotomy or arthroscopy.\(^{49,50}\) However, AMIC is more cost-effective, since it requires only one surgical step, avoiding in vitro cell expansion. Moreover, along with the avoidance of chondrocyte harvesting, AMIC should lead to less morbidity and faster recovery. These features make AMIC attractive to both surgeons and patients. We were unable to identify clinical studies which directly compare AMIC versus mACI for chondral defects of the knee:
| Author, year | Journal                  | Study Design | Follow-up (months) | Treatment | Procedures Female (%) | Mean age | Mean BMI |
|--------------|--------------------------|--------------|--------------------|-----------|-----------------------|----------|----------|
| Akgun et al. 2015 28 | Arch Orthop Trauma Surg | Prospective, Randomized | 24                 | Control Group | mACI                 | 7        | 57       | 32       | 24.1     |
| Anders et al. 2013 64 | Open Orthop J            | Prospective, Randomized | 24                 | AMIC       | Control Group         | 8        | 12       | 35       | 27.4     |
| Astur et al. 2018 65 | Rev Bras Ortoph          | Prospective   | 12                 | AMIC       | Control Group         | 7        | 14       | 37       |          |
| Bartlett et al. 2005 | J Bone Joint Surg        | Prospective, Randomized | 12                 | AMIC       | Control Group         | 44       | 41       |          |          |
| Basad et al. 2010 27 | Knee Surg Sports Traumatol Arthrosc | Prospective, Randomized | 24                 | AMIC       | Control Group         | 40       | 38       | 33       | 25.3     |
| Basad et al. 2015 15 | Knee Surg Sports Traumatol Arthrosc | Prospective, Randomized | 60                 | AMIC       | Control Group         | 25       | 37       | 32       | 24.0     |
| Bocher et al. 2017 54 | J Orthop Surg Res       | Prospective, Randomized | 36                 | AMIC       | Control Group         | 25       | 16       | 34       | 25.6     |
| Behrens et al. 2006 23 | Knee                     | Prospective   | 35                 | AMIC       | Control Group         | 38       | 50       | 35       |          |
| Britberg et al. 2018 86 | Am J Sports Med          | Prospective, Randomized | 60                 | AMIC       | Control Group         | 65       | 38       | 35       |          |
| Chung et al. 2014 57 | Knee Surg Sports Traumatol Arthrosc | Prospective | 24                 | Control Group | AMIC     | 12       | 83       | 44       |          |
| Cvitdanovich et al. 2017 68 | Am J Sports Med          | Prospective   | 24                 | Control Group | AMIC     | 24       | 42       | 47       |          |
| De Girolamo et al. 2019 47 | J Clin Med              | Prospective, Randomized | 100                | AMIC       | Control Group         | 12       | 38       | 30       |          |
| Ebert et al. 2011 31 | Am J Sports Med          | Prospective   | 60                 | mACI       | Control Group         | 44       | 48       | 39       | 25.5     |
| Ebert et al. 2012 56 | Arthroscopy              | Prospective   | 24                 | mACI       | Control Group         | 20       | 50       | 24       | 26.6     |
| Ebert et al. 2015 69 | Am J Sports Med          | Prospective   | 24                 | mACI       | Control Group         | 10       | 20       | 39       | 25.8     |
| Ebert et al. 2017 70 | Am J Sports Med          | Prospective   | 60                 | mACI       | Control Group         | 31       | 51       | 35       | 26       |
| Efe et al. 2011 71 | Am J Sports Med          | Prospective   | 24                 | mACI       | Control Group         | 15       | 60       | 26       |          |
| Enea et al. 2013 72 | Knee                     | Retrospective | 22                 | AMIC       | Control Group         | 9        | 45       | 48       |          |
| Enea et al. 2015 73 | Knee                     | Retrospective | 29                 | AMIC       | Control Group         | 9        | 44       | 43       |          |
| Ferruzzi et al. 2008 74 | J Bone Joint Surg       | Prospective   | 60                 | Control Group | mACI     | 48       | 38       | 32       |          |
| Gille et al. 2013 73 | Arch Orthop Trauma Surg | Prospective   | 24                 | AMIC       | Control Group         | 57       | 33       | 37       |          |
| Gobbi et al. 2009 76 | Am J Sports Med          | Prospective   | 60                 | mACI       | Control Group         | 34       | 32       | 31       |          |
| Gudas et al. 2018 77 | J Orthop Surg           | Retrospective | 54                 | AMIC       | Control Group         | 15       | 33       | 31       |          |
| Hoffburg et al. 2019 33 | Orthop J Sports Med     | Prospective   | 63                 | mACI       | Control Group         | 29       | 48       | 16       | 21.3     |
| Kon et al. 2011 61 | Am J Sports Med          | Prospective   | 61                 | Control Group | mACI     | 22       | 32       | 24       | 24.7     |
| Lahner et al. 2018 78 | Biomed Res Int          | Prospective   | 15                 | AMIC       | Control Group         | 9        | 48       | 29.3     |          |
| Lopez-Alcorocho et al. 2018 79 | Cartilage              | Prospective   | 24                 | mACI       | Control Group         | 50       | 30       | 35       |          |
| Macnill et al. 2011 80 | Int Orthop              | Prospective   | 66                 | Control Group | mACI     | 24       | 29       | 16       |          |
| Macnill et al. 2012 81 | Am J Sports Med         | Prospective   | 45                 | Control Group | mACI     | 25       | 80       | 35       |          |
| Marlovits et al. 2012 82 | Am J Sports Med         | Prospective   | 60                 | mACI       | Control Group         | 24       | 12       | 35       |          |
| Meyerkort et al. 2014 83 | Knee Surg Sports Traumatol Arthrosc | Prospective | 60                 | mACI       | Control Group         | 23       | 42       |          |          |
| Migliorini et al. 2021 84 | LIFE                    | Prospective   | 43.7               | AMIC       | Control Group         | 32       | 35       | 27.1     |          |
| Migliorini et al. 2021 85 | LIFE                    | Prospective   | 45.1               | AMIC       | Control Group         | 27       | 48       | 36       | 26.9     |
| Nawaz et al. 2014 32 | J Bone Joint Surg       | Retrospective | 74                 | Control Group | mACI     | 827      | 40       | 34       |          |

(Continued)
Table 1 Continued.

| Author, year            | Journal                                | Study Design       | Follow-up (months) | Treatment | Procedures | Female (%) | Mean age | Mean BMI |
|-------------------------|----------------------------------------|--------------------|--------------------|-----------|------------|------------|----------|----------|
| mACI                    | Nejadnik et al. 2010                   | Retrospective      | 24                 | mACI      | Control Group | 36         | 50       | 43       |
|                         | Niemeyer et al. 2008                   | Retrospective      | 38                 | mACI      | Control Group | 36         | 44       | 44       |
|                         | Niemeyer et al. 2016                   | Am J Sports Med    | 12                 | mACI      | Control Group | 25         | 33       | 33       |
|                         | Niemeyer et al. 2019                   | Arch Orthop Trauma Surg | Prospective, Randomized | 12 | mACI | 25 | 16 | 34 | 25.6 |
|                         | Saris et al. 2014                      | Am J Sports Med    | 24                 | mACI      | Control Group | 72         | 37       | 35       |
|                         | Schagemann et al. 2018                 | Arch Orthop Trauma Surg | Retrospective | 24 | AMIC | 20 | 35 | 38 | 27.0 |
| Schiavone Panni et al. 2018 | Knee Surg Sports Traumatol Arthrosc | Retrospective | 84 | AMIC | 21 |        |        |        |        |
| Schneider et al. 2011   | Am J Sports Med                        | Prospective        | 30                 | mACI      | Control Group | 116        | 42       | 33       |
| Schütter et al. 2019    | Arch Orthop Trauma Surg                | Prospective        | 60                 | mACI      | Control Group | 23         | 34       | 27.8    |
| Seibold et al. 2018     | Knee Surg Sports Traumatol Arthrosc    | Prospective        | 35                 | mACI      | Control Group | 30         | 36       | 36       |
| Steinwachs et al. 2019  | Knee                                    | Prospective        | 6                  | AMIC      | Control Group | 93         | 28       | 42       |
| Vole et al. 2017        | Int Orthop                              | Prospective, Randomized | 60 | AMIC | 17 | 29 | 34 | 27.4 |
| Zeilang et al. 2010     | Am J Sports Med                        | Prospective, Randomized | 24 | mACI | 11 | 45 | 29 | 25.0 |

Table 2 Characteristics of the two cohorts at baseline (n.s.: not significant)

| Endpoint                      | AMIC (n = 373) | mACI (n = 1237) | P  |
|-------------------------------|----------------|-----------------|----|
| Follow-up (months)            | 37.8 ± 29.9    | 39.8 ± 17.2     | n.s.|
| Women                         | 34% (125 of 373) | 37% (455 of 1237) | n.s.|
| Mean age                      | 28.2 ± 6.0     | 33.5 ± 6.5      | n.s.|
| Mean BMI                      | 26.1 ± 1.6     | 25.9 ± 1.2      | n.s.|
| Right side                    | 33% (124 of 373) | 52% (643 of 1237) | n.s.|
| Defect size (cm²)             | 3.5 ± 0.9      | 3.8 ± 1.0       | n.s.|
| VAS                           | 6.4 ± 0.9      | 5.6 ± 1.1       | n.s.|
| Tegner                        | 4.0 ± 1.4      | 3.1 ± 1.3       | n.s.|
| Lysholm                       | 54.1 ± 12.6    | 53.7 ± 10.7     | n.s.|
| IKDC                          | 47.0 ± 9.1     | 40.2 ± 8.3      | n.s.|

Table 3 Results of Tegner and IKDC scores (n.s.: not significant)

| Endpoint | AMIC | mACI | MD | P  |
|----------|------|------|----|----|
| VAS      | 2.8 ± 2.2 | 2.9 ± 1.3 | 0.07 | n.s.|
| Tegner   | 4.4 ± 0.6 | 4.7 ± 0.8 | 0.3  | n.s.|
| Lysholm  | 81.9 ± 7.1 | 65.7 ± 28.2 | 1f  | 0.02|
| IKDC     | 79.2 ± 10.4 | 71.5 ± 6.3 | 7.7  | 0.03|

this is the single most important limitation of the available literature. Future studies should establish the most appropriate strategy for knee chondral defects. We hypothesize that the AMIC procedure will promote faster recovery and result in higher patient satisfaction.

We point out that all statistical analyses were performed regardless of the surgical approach.
**Conclusion**

AMIC may provide better outcomes than mACI for chondral defects of the knee. Further studies are needed to validate these results in a clinical setting.

**Conflict of interest statement**

The authors have no potential conflicts of interest.

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**Ethical approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent**

For this type of study informed consent is not required.

**Data availability**

The data underlying this article are available in the article and in its online supplementary material.

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