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Autologous Matrix-Induced Chondrogenesis

A Systematic Review of the Clinical Evidence

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Background: The addition of a type I/III collagen membrane in cartilage defects treated with microfracture has been advocated for cartilage repair, termed ''autologous matrix-induced chondrogenesis'' (AMIC).

Purpose: To examine the current clinical evidence regarding AMIC for focal chondral defects.

Study Design: Systematic review.

Methods: A systematic review was performed by searching PubMed, ScienceDirect, and Cochrane Library databases. Inclusion criteria were clinical studies of AMIC for articular cartilage repair, written in English. Relative data were extracted and critically analyzed. PRISMA guidelines were applied, the methodological quality of the included studies was assessed by the modified Coleman Methodology Score (CMS), and aggregate data were generated.

Results: Twenty-eight clinical articles were included: 12 studies (245 patients) of knee cartilage defects, 12 studies (214 patients) of ankle cartilage defects, and 4 studies (308 patients) of hip cartilage defects. The CMS demonstrated a suboptimal study design in the majority of published studies (knee, 57.8; ankle, 55.3; hip, 57.7). For the knee, 1 study reported significant clinical improvements for AMIC compared with microfracture for medium-sized cartilage defects (mean defect size 3.6 cm^2) after 5 years (level of evidence, 1). No study compared AMIC with matrix-assisted autologous chondrocyte implantation (ACI) in the knee. For the ankle, no clinical trial was available comparing AMIC versus microfracture or ACI. In the hip, only one analysis (level of evidence, 3) compared AMIC with microfracture for acetabular lesions. For medium-sized acetabular defects, one study (level of evidence, 3) found no significant differences between AMIC and ACI at 5 years. Specific aspects not appropriately discussed in the currently available literature include patient-related factors, membrane fixation, and defect properties. No treatment-related adverse events were reported.

Conclusion: This systematic review reveals a paucity of high-quality, randomized controlled studies testing the AMIC technique versus established procedures such as microfracture or ACI. Evidence is insufficient to recommend joint-specific indications for AMIC. Additional nonbiased, high-powered, randomized controlled clinical trials will provide better clinical and structural long-term evidence, thus helping to define possible indications for this technique.

Keywords: systematic review; autologous matrix-induced chondrogenesis; microfracture; collagen membrane; scaffold; cartilage repair

Two currently available, major clinical options for the repair of symptomatic chondral lesions are marrow stimulation techniques that include microfracture for small defects and matrix-assisted autologous chondrocyte implantation (ACI) for larger defects.[28,53] With marrow stimulation techniques, the cartilage defect is filled with a bone marrow clot containing mobilized pluripotent mesenchymal stem cells (MSCs), resulting in the subsequent formation of a cartilaginous repair tissue.[23] For large defect areas, clinical evidence suggests that a satisfactory chondrogenesis solely based on marrow stimulation may be difficult to achieve. Recently, the additional introduction of a solid acellular type I/III collagen membrane in cartilage defects after treatment with microfracture has been advocated, a combined

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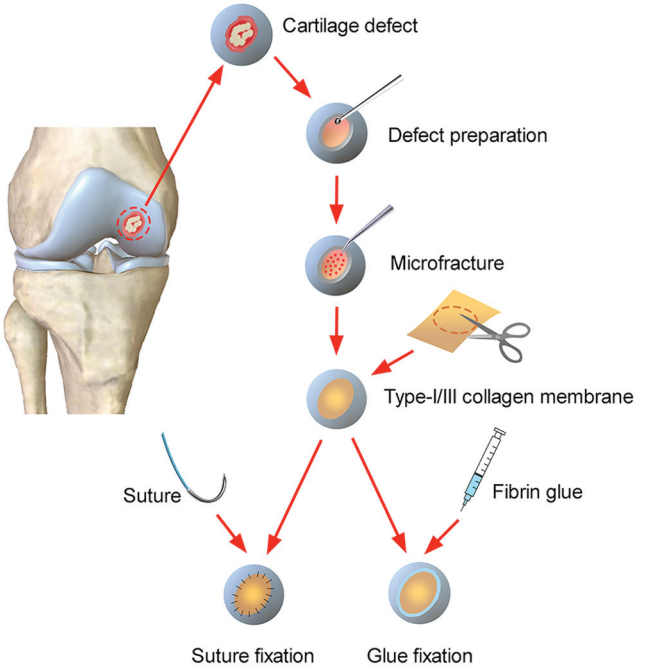

Figure 1. Autologous matrix-induced chondrogenesis (AMIC). Following a diagnostic arthroscopy, the AMIC procedure is performed with either an arthrotomy or arthroscopy. The defect is meticulously prepared, and minute subchondral bone penetrations are induced by microfracture. The type I/III collagen membrane is implanted with its porous layer facing the subchondral bone. Fixation is usually achieved with sutures (size USP 6.0) or with fibrin glue.[22]

approach termed "autologous matrix-induced chondrogenesis" (AMIC).[6,7,32] (AMIC should not be confused with MACI, an abbreviation for "matrix-assisted ACI.") Although both ACI and AMIC entail the implantation of a biomaterial matrix, AMIC does not include the use of autologous articular chondrocytes (such as those that are attached to the biomaterial membrane in the ACI technique). Of similar importance, ACI should never include the penetration of the subchondral bone plate (microfracture) as mandatory for AMIC. AMIC has been promoted as both an extension of the microfracture technique and a low-cost alternative to matrix-assisted ACI, particularly for medium-sized defects.[8] The advertised advantages are a possible stabilization of the so-called super-clot within the cartilage defect following microfracture and an improved cartilage repair.[6,36]

Following a diagnostic arthroscopy, the AMIC technique is performed with either an arthrotomy or arthroscopy (Figure 1). The cartilage defect is always prepared by removing loose cartilage flaps, debriding the calcified cartilage layer down to the subchondral bone plate, and establishing a stable defect rim. Next, a standard microfracture procedure is performed, inducing subchondral bone plate penetrations. A type I/III collagen membrane is trimmed to match the defect size and then implanted. Fixation of the membrane may be achieved with sutures or autologous fibrin glue.[22]

AMIC is a registered trademark of a company providing a proprietary type I/III collagen membrane. The term "AMIC" suggests an active propagation of MSC chondrogenesis by the implanted medical device.[33] Nevertheless, the current in vitro and preclinical in vivo evidence supporting the concept that such solid acellular type I/III collagen scaffolds may be superior to classic approaches to induce in vitro or in vivo chondrogenesis of MSCs is weak.[23] Despite the increasing clinical interest and use of this technique in recent years, a systematic examination of the currently available clinical evidence has, to the best of our knowledge, not yet been performed.

This systematic review examines the current evidence for possible chondrogenic effects of such a type I/III collagen biomaterial in a joint-specific fashion. The following 3 questions were addressed: (1) Does AMIC show superior clinical outcomes in long-term follow-up compared with microfracture alone? (2) Does AMIC show similar or superior clinical outcomes in long-term follow-up compared with ACI? (3) Do specific aspects (eg, lesion characteristics or membrane fixation) influence the clinical outcome of AMIC?

METHODS

Search Strategy

A systematic literature search was performed in the PubMed, ScienceDirect, and Cochrane Library databases up to September 1, 2017, by use of the terms "AMIC," "autologous matrix-induced chondrogenesis," and "type I/III collagen scaffold." Studies were included if they fulfilled the following criteria: (1) clinical studies with measures of the repair tissue or functional outcome; (2) studies involving cartilage defects of shoulder, hip, knee, and ankle; and (3) articles in English language. Two reviewers independently screened all articles, and disagreement was resolved by consultation with a third reviewer. All abstracts and titles of the studies were initially screened. Full texts were then obtained for all studies meeting the inclusion criteria and were reviewed to reconfirm their eligibility.

Data Extraction and Critical Appraisal

The data extracted included funding source, level of evidence, number of patients, sex ratio (male/female), patient age, defect characteristics (location, number of defects per patient, defect type and size), treatment groups, collagen scaffold characteristics, manufacturer name, scaffold fixation, postoperative rehabilitation, follow-up, outcome evaluation, and main outcome. Data were collected by 1 reviewer in a standardized extraction form and verified by the other 2 reviewers to reach a consensus. Due to the methodological heterogeneity for the clinical outcome assessment in the included studies, only the data from outcome measures with proven validity and reliability were further selected and aggregated. For the knee, these included the visual analog scale (VAS) for pain, Lysholm score, Tegner activity scale, Knee injury and Osteoarthritis

TABLE 1
Modified Coleman Methodology Score (CMS) for Studies Reporting the Outcomes of Autologous Matrix-Induced Chondrogenesis

Criteria	Score
Part A: Only 1 score to be given for each of the 7 sections.	
1. Study size	
• >60	10
• 41-60	7
• 20-40	4
• <20, not stated	0
2. Mean duration of follow-up	
• >24 months	5
• 12-24 months	2
• <12 months, not stated, or unclear	0
3. Number of treatment procedures	
• One surgical procedure only	10
• More than 1 surgical procedure, but >90% of subjects undergoing the 1 procedure	7
• Not stated, unclear, or <90% of subjects undergoing the 1 procedure	0
4. Type of study	
• Randomized controlled trial	10
• Cohort study	5
• Case series or case reports	0
5. Diagnostic certainty	
• In all	5
• In ≥80%	3
• In <80%	0
6. Description of surgical procedure	
• Adequate (technique stated and necessary details of that type of procedure given)	10
• Fair (technique only stated without elaboration)	5
• Inadequate, not stated, or unclear	0
7. Description of postoperative rehabilitation	
• Well described with >80% of patients complying	10
• Well described with 60%-80% of patients complying	5
• Protocol not reported or ≤60% of patients complying	0
Part B: Scores may be given for each option in each of the 3 sections if applicable.	
1. Outcome criteria	
• Outcome measured clearly	2
• Timing of outcome assessment clearly stated	2
• Reported interrater or intrarater reliability	3
• Use of outcome criteria that has reported good reliability	3
2. Procedure for assessing outcomes	
• Subjects recruited	5
• Investigator independent of surgeon/therapist	4
• Written assessment	3
• Completion of assessment by subjects themselves with minimal investigator assistance	3
3. Description of subject selection process	
• Selection criteria reported and unbiased	5
• Recruitment rate reported	
◦ >80%	5
◦ <80%	3
• Eligible subjects not included in the study accounted for, or 100% recruitment	5
Maximum (Part A)	60
Maximum (Part B)	40
Maximum (CMS)	100

Outcome Score (KOOS), and MOCART (magnetic resonance observation of cartilage repair tissue) score. For the ankle, results of the VAS, American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score, Tegner activity scale, Foot Function Index (FFI)–German version, and MOCART score were specified. For the hip,

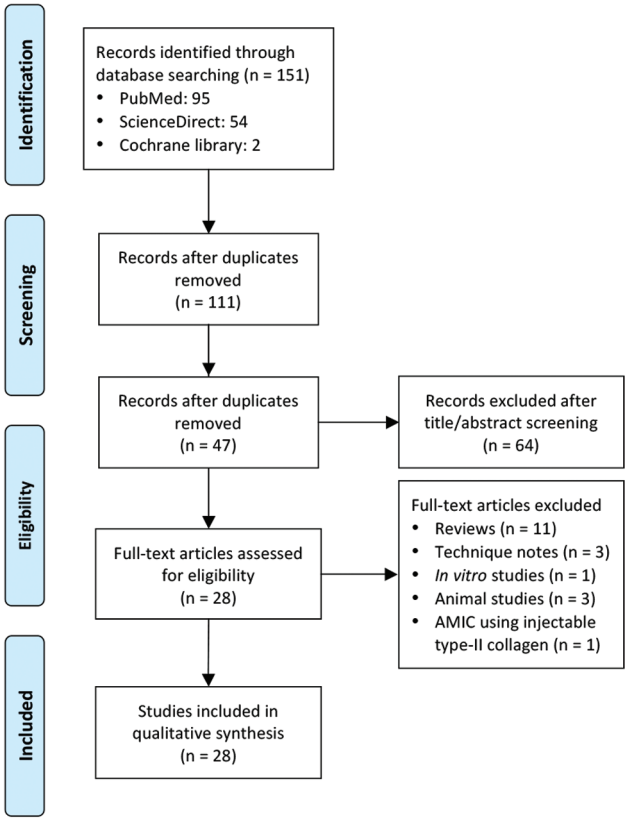

Figure 2. Study selection flow diagram according to the PRISMA guidelines (Preferred Reporting Items for Systematics Reviews and Meta-Analyses).[42]

the modified Harris hip score (mHHS), Oxford hip score, University of California at Los Angeles (UCLA) activity score, and MOCART score were summarized. The aggregated data were reported in the chronological pattern including preoperative range (if available) and 4 postoperative times (if available).

Methodological Assessment

All included articles were assessed independently by 2 reviewers with a modified version of the Coleman Methodology Score (CMS) (Table 1).[11] The reviewers compared their scores and discussed them until a consensus was achieved. Each study was scored for each of the 10 criteria from 2 parts of the grading system (part A, 7 criteria; part B, 3 criteria).

RESULTS

Search Results and Characteristics of Included Studies

A total of 151 papers were identified. After duplicates were removed, 111 articles fulfilled the inclusion criteria (Figure 2). After the titles, abstracts, and full text of the articles were screened with the aforementioned criteria, 28 clinical

TABLE 2
Mean Scores for the 10 Criteria of the Coleman Methodology Score (CMS) for Studies of AMIC for Articular Cartilage Repair in Knee, Ankle, and Hip Joints[a]

	Knee		Ankle		Hip		All Joints	
Criteria	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Part A								
1. Study size	2.5 (2.8)	0-7	2.2 (3.1)	0-10	6.0 (3.5)	4-10	2.7 (3.1)	0-10
2. Mean duration of follow-up	3.2 (2.0)	0-5	2.6 (2.3)	0-5	3.3 (2.9)	0-5	2.9 (2.2)	0-5
3. No. of treatment procedures	8.9 (3.9)	0-10	7.5 (4.5)	0-10	8.3 (2.9)	5-10	8.2 (3.7)	0-10
4. Type of study	2.3 (4.1)	0-10	0.4 (1.4)	0-5	4.0 (3.6)	0-7	1.6 (3.3)	0-10
5. Diagnostic certainty	5.0 (0)	5	5.0 (0)	5	5.0 (0)	5	5.0 (0)	5
6. Description of surgical procedure	9.6 (1.4)	5-10	9.2 (2.9)	0-10	6.7 (2.9)	5-10	9.1 (2.4)	0-10
7. Description of postoperative rehabilitation	7.5 (4.5)	0-10	8.3 (3.9)	0-10	8.0 (3.5)	4-10	7.9 (4.0)	0-10
Total score (part A)	38.9 (8.9)	30-57	35.2 (7.6)	24-49	41.3 (12.2)	28-52	37.5 (8.6)	24-57
Part B								
1. Outcome criteria	7.0 (0)	7	7.0 (0)	7	5.3 (1.5)	4-7	6.8 (0.7)	4-7
2. Procedure for assessing outcomes	6.6 (2.5)	0-8	7.8 (1.4)	6-11	4.3 (1.2)	3-5	6.9 (2.2)	0-11
3. Description of subject selection process	5.3 (0.9)	5-8	5.3 (0.9)	5-8	6.7 (2.9)	5-10	5.4 (1.2)	5-10
Total score (part B)	18.8 (2.4)	12-20	20.1 (1.7)	17-23	16.3 (5.1)	12-22	19.1 (2.7)	12-23
Total CMS	57.8 (9.9)	44-77	55.3 (7.1)	44-66	57.7 (12.7)	43-64	56.6 (8.7)	43-77

[a]AMIC, autologous matrix-induced chondrogenesis; SD, standard deviation. Total CMS score ranges from 0 to 100, and a score of 100 represents a perfectly designed study excluding any kind of biases. For detailed additional information on each of the individual studies, refer to Appendix Table A4, available online.

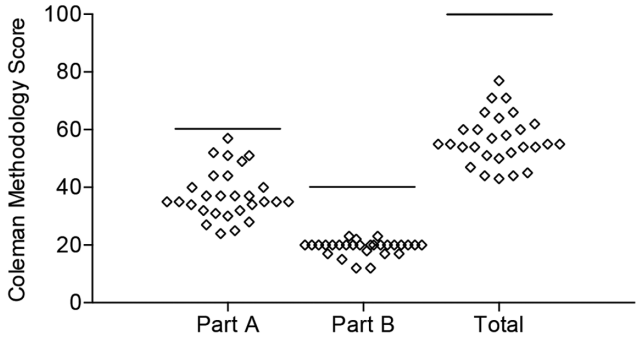

Figure 3. Dot plot showing the results of Coleman Methodology Score (CMS) of the included studies. The lines above the dots indicate the maximum scores of part A, part B, and total CMS.

articles were finally included: 12 studies involving 245 patients with knee cartilage defects (Appendix Table A1, available in the online version of this article), 12 studies involving 214 patients with ankle defects (Appendix Table A2, available online), and 4 studies recruiting 308 patients with defects of the acetabulum and femoral head (Appendix Table A3, available online).

Of the 13 identified observational studies with defects solely treated by AMIC, 2 articles were reports of single cases[4,48] and 11 were case series comprising a total of 253 patients (Appendix Tables A1-A3, available online).[§] Of the 11 identified clinical articles about AMIC combined with other materials or surgical procedures, 4 articles were reports of single cases[14,40,55,57] and 7 were case series of a total of 335 patients.[13,16,20,46,50,52,58] Only 3 studies compared the outcomes of AMIC with microfracture: 1 study of the hip[21] and 2 studies of the knee.[1,54] Only 1 study of the hip compared the outcomes between AMIC and matrix-assisted ACI.[37]

Methodology Quality Assessment With the Coleman Methodology Score

The CMS evaluates the quality of the method, with a score ranging from 0 to 100. The maximal score of 100 indicates a study design that essentially avoids the influence of chance errors, biases, and confounding factors. The overall mean CMS of the included AMIC studies was 56.6 (range, 43-77) (Table 2). The mean total CMS was 57.8 (range, 44-77) for the knee, 55.3 (range, 44-66) for the ankle, and 57.7 (range, 43-77) for the hip. The mean total score of parts A and B of the CMS was 37.5 (range, 24-57) and 19.1 (range, 12-23), respectively (Figure 3). Major areas of methodological deficiencies were study size (mean 2.7; range, 0-10), type of study (mean 1.6; range, 0-10), and description of subject selection process (mean 5.4; range, 5-10) (Appendix Table A4, available online).

Reported Outcomes of AMIC in the Knee

In the majority of the studies, patients experienced decreased pain on the VAS, with ranges of 0-10 preoperatively to 0-3 within 5 years postoperatively (Table 3) following AMIC alone or combined with other biomaterials or

[§]References 12, 15, 24, 25, 29, 31, 32, 34, 47, 51, 56.

TABLE 3
Aggregate Data of Outcome Measures of AMIC in the Knee[a]

Outcome Measures	Normal Range	No. of Patients[b]	Lesion Size, cm^2	Preoperative Range	Postoperative Follow-up Range				References
					≤1 year	1-2 years	2-5 years	≥5 years	
VAS for pain	0-10	(A) 161 (C) 10	2.0-6.0	1-10	0-9	0-9	0-3	NA	1, 14-16, 24, 32, 46
Lysholm knee score	0-100	(A) 146 (C) 0	2.0-8.0	9-79	39-100	27-100	25-69	53-92	4, 14, 25, 32, 47, 48
Tegner activity scale	0-10	(A) 108 (C) 10	2.0-6.0	NA	1-7	1-4	4	NA	15, 16, 25, 32
KOOS Pain	0-100	(A) 28 (C) 0	2.0-6.0	39-92	50-86	61-97	NA	NA	15, 16, 46, 48
KOOS Symptoms/Stiffness	0-100	(A) 28 (C) 0	2.0-6.0	36-86	43-86	75-100	NA	NA	15, 16, 46, 48
KOOS ADL	0-100	(A) 28 (C) 0	2.0-6.0	38-76	34-96	62-97	NA	NA	15, 16, 46, 48
KOOS Sports	0-100	(A) 28 (C) 0	2.0-6.0	0-20	5-50	10-45	NA	NA	15, 16, 46, 48
KOOS QOL	0-100	(A) 28 (C) 0	2.0-6.0	19-31	13-69	38-56	NA	NA	15, 16, 46, 48
MOCART score	0-100	(A) 27 (C) 0	2.0-6.0	NA	40-76	31-77	NA	NA	15, 16, 46

[a]High values reflect good results for all scores with the exception of the VAS, for which low values reflect good results. The majority of the data given here originate from studies without control groups. Although it is recommended to report the KOOS subscales rather than a mean value of all KOOS subscales, the data in 2 studies[15,46] are not presented in such a way. Some studies[25,32,47] described a MOCART score evaluation in the Material and Methods but did not report numerical MOCART data. For detailed additional information on each of the individual studies, please refer to Appendix Table A1, available online. ADL, activities of daily life; AMIC, autologous matrix-induced chondrogenesis; KOOS, Knee injury and Osteoarthritis Outcome Score; MOCART, magnetic resonance observation of cartilage repair tissue; NA, not available; QOL, quality of life; VAS, visual analog scale.

[b](A) AMIC; (C) control group.

procedures.[1,14-16,24,32,46] Patients mostly reported improved knee functional scores within the first 2 years after treatments. The range of Lysholm score improved from 9-79 preoperatively to 27-100 within the first 2 years, declined to 25-69 between 2 and 5 years, and increased to 53-92 beyond 5 years.[4,14,25,32,47,48] The range of the MOCART score was 40-76 at the first postoperative year and 31-77 at the second postoperative year.[15,16,46] No long-term data regarding the KOOS and MOCART scores beyond the second postoperative year were available.

A randomized controlled bicenter trial (level 1) compared AMIC with microfracture.[1] Thirty-eight patients (age 21-50 years, mean defect size ~3.4 cm^2) were treated either with (1) microfracture, (2) sutured AMIC, or (3) glued AMIC. For all 3 groups, no significant differences were found at 1 and 2 years postoperatively regarding improvements in the modified Cincinnati and International Cartilage Repair Society (ICRS) scores.[1] The same authors reported 5-year outcomes of 39 patients (age 37 ± 10 years; mean defect size 3.6 ± 1.6 cm^2) similarly randomized in a prospective bicenter clinical trial.[54] The modified Cincinnati score was stable in both AMIC groups, whereas it significantly decreased in the microfracture group. The modified ICRS score for pain was significantly reduced in all groups without significant differences. Individual magnetic resonance imaging (MRI) assessments showed satisfactory defect filling in the majority of cases. Although defect filling per MRI was reported to be more complete in the AMIC group, no statistically significant differences were reported. No MOCART score evaluation was performed. Histological evaluation of biopsy specimens obtained after 2 years in 2 patients demonstrated a fibrocartilaginous repair tissue without evidence of a residual membrane.

Reported Outcomes of AMIC in the Ankle

Significant pain relief was reported in all studies involving ankle cartilage defects treated with AMIC, as VAS decreased from 2-9 preoperatively to 0-3 within 5 years postoperatively (Table 4).[12,13,31,40,50-52,55-58] AOFAS ankle and hindfoot score improved from 17-79 preoperatively to 79-86 within 5 years postoperatively (applied in 11 of the 12 studies).[12,13,40,50-52,55-57] MOCART scoring was reported in only 6 of 12 studies. Values increased from 19-66 at the first postoperative year to 20-95 within 5 postoperative years.[29,31,50,52,56,58] No clinical trial was identified comparing clinical outcomes of AMIC versus microfracture or ACI.

Reported Outcomes of AMIC in the Hip

Reported outcomes on hip function (including pain) as determined by the mHHS improved from ranges of 39-51 preoperatively to 72-89 within the first postoperative year and were maintained with 72-91 beyond 5 postoperative years (Table 5).[20,21,37] A range of the MOCART score

TABLE 4
Aggregate Data of Outcome Measures of AMIC in the Ankle[a]

Outcome Measures[b]	Normal Range	No. of Patients[c]	Lesion Size, cm^2	Preoperative Range	Postoperative Range at Follow-up				References
					≤1 year	1-2 years	2-5 years	≥5 years	
VAS for pain	0-10	(A) 190 (C) 0	1.0-3.0	2-9	0-5	0-7	0-3	NA	12, 13, 31, 40, 50-52, 55-58
AOFAS ankle-hindfoot score	0-100	(A) 116 (C) 0	1.0-3.0	17-79	66-100	61-100	79-86	NA	12, 13, 40, 50-52, 55-57
Tegner activity scale	0-10	(A) 61 (C) 0	1.5	6	6	NA	1-6	NA	40
Activity rating scale	0-16	(A) 60 (C) 0	NA	NA	NA	NA	2-3	NA	58
FFI–German version	0-100	(A) 21 (C) 0	1.5	38-74	8-58	NA	3-45	NA	29
MOCART score	0-100	(A) 167 (C) 0	1.0-2.0	NA	40-76	31-77	NA	NA	29, 31, 50, 52, 56, 58

[a]AMIC, autologous matrix-induced chondrogenesis; AOFAS, American Orthopaedic Foot and Ankle Society; FFI, Foot Function Index; MOCART, magnetic resonance observation of cartilage repair tissue; NA, not available; VAS, visual analog scale.
[b]High values reflect good results for all scores with the exception of the VAS and FFI, for which low values reflect good results. All data given here originate from studies without control groups. For detailed additional information on each of the individual studies, please refer to Appendix Table A2, available online.
[c](A) AMIC; (C) control group.

TABLE 5
Aggregate Data of Outcome Measures of AMIC in the Hip[a]

Outcome Measures[b]	Normal Range	No. of Patients[c]	Lesion Size, cm^2	Preoperative Range	Postoperative Range at Follow-up				References
					≤1 year	1-2 years	2-5 years	≥5 years	
Modified HHS	0-91	(A) 302 (C) 103	2.0-8.0	39-51	72-89	NA	78-91	72-91	20, 21, 37
Oxford hip score	0-100	(A) 6 (C) 0	1.0-12.0	NA	NA	13-17	NA	NA	34
UCLA activity score	1-10	(A) 6 (C) 0	1.0-12.0	NA	NA	5-10	NA	NA	34
MOCART score	0-100	(A) 6 (C) 0	1.0-12.0	NA	NA	55-75	NA	NA	34

[a]AMIC, autologous matrix-induced chondrogenesis; HHS, Harris hip score; MOCART, magnetic resonance observation of cartilage repair tissue; NA, not available; T, year(s) of follow-up; UCLA, University of California at Los Angeles.
[b]High values of all scores reflect good results. No numerical data of the visual analog scale are provided in any of the 4 studies. The mHHS is categorized as excellent (81-91), good (71-80), fair (61-70), and poor (≤60). For detailed additional information on each of the individual studies, please refer to Appendix Table A3, available online.
[c](A) AMIC; (C) control group.

was reported only in 1 study at 1 time point (55-57; 1-2 postoperative years).[34]

Fontana et al[21] published a retrospective analysis of a consecutive single-center series of patients in which the authors compared AMIC and microfracture for acetabular chondral lesions induced by femoroacetabular impingement (FAI). Patients (age 18-55 years; defect size 2.0-8.0 cm^2 including concomitant chondral lesions of the femoral head; Outerbridge grade III-IV) were treated by microfracture (n = 77) or AMIC (n = 70). Clinical outcome as assessed by the mHHS was significantly improved in both groups at 6 months postoperatively (AMIC, 68-96; microfracture, 58-98). Between 2 and 5 years postoperatively, the mHHS remained stable in the AMIC group and gradually deteriorated in the microfracture group (to 48-92).[21]

The only trial comparing clinical outcomes of arthroscopic matrix-assisted ACI (n = 26) with AMIC (n = 31) for the treatment of acetabular chondral defects (range, 2.0-4.0 cm^2) resulting from FAI was a retrospective, nonrandomized, single-center study published by Mancini and Fontana.[37] Both treatment groups showed significant improvements of the mHHS over baseline levels up to 3 years postoperatively, which remained stable until the 5-year follow-up (matrix-assisted ACI, 37.8; AMIC, 39.1) without significant differences between groups. It is unclear

whether the mHHS score between the groups was significantly different between the postoperative time points. No other knee function scores or MOCART score data were provided. The authors reported no treatment-related complications (including conversion to total hip arthroplasty) and no adverse effects within 5 years postoperatively.

Specific Aspects Possibly Influencing the Clinical Outcome of AMIC

No influences of patient age,[12] body mass index, and number of previous operations were reported.[25] Male patients showed significantly higher values on the ICRS score compared with females. Regarding the nature of the defect, Kusano et al[32] noted more pronounced improvements in clinical outcome scores for osteochondral compared with chondral defects in the knee. A subgroup analysis within the study comparing AMIC with microfracture for acetabular chondral defects revealed more pronounced differences for defects 4 cm^2 or larger.[21] A similar subgroup analysis within the study comparing matrix-assisted ACI and AMIC for acetabular chondral defects larger than 3 cm^2 yielded similar clinical results.[37] No study found an effect of the fixation technique.

Treatment-Related Adverse Events, Reoperations, and Complications

No treatment-related adverse events were reported. The reoperation rate following AMIC was 5 of 245 in the knee, 1 of 214 in the ankle, and 1 of 308 in the hip. Revision chondroplasty ("shaving") was most often performed, mainly indicated to remove intralesional osteophytes (4/566).[15,16] Conversions to total joint arthroplasty occurred in 2 cases (of 566).[25] Other complications included joint stiffness (9/566),[32] increased pain (3/566),[1,34] joint catching (3/566),[15,16] joint impingement (1/566),[50] joint effusion (1/566),[25] joint instability (1/566),[40] hematoma (1/566),[32] muscle vein thrombosis (1/566),[25] and muscle hypotrophy (1/566).[48] Yet, 18 of 28 publications did not report on complications.

DISCUSSION

The most important finding of this systematic review is the paucity of high-quality, randomized controlled studies testing the AMIC technique versus established cartilage repair options. Specifically, no randomized controlled study for the knee is available comparing AMIC with microfracture for chondral defects smaller than 3.0 cm^2, the classic indication for microfracture. For knee cartilage defects with a mean defect size of 3.6 cm^2, significant clinical improvements were reported for AMIC compared with microfracture after 5 years in a study with level of evidence 1. No clinical trial is available comparing AMIC with ACI in the knee. For ankle cartilage defects, no study compared AMIC versus either microfracture or ACI. For acetabular chondral lesions, 1 study with a level of evidence 3 found significantly improved clinical parameters for AMIC compared with microfracture. Another study with level of evidence 3 found no significant differences between AMIC and ACI at 5 years for medium-sized acetabular chondral defects.

Basic Science of AMIC

A recent review of the currently available in vitro and translational in vivo data on solid acellular type I/III collagen biomaterials as used for AMIC did not provide sufficient evidence that such a matrix alone may induce chondrogenesis.[23] The data from a few in vitro studies comparing type I with type II collagen matrices suggest better chondrogenesis with type II collagen scaffolds. In vivo, 1 long-term study in sheep showed that AMIC significantly enhanced the cartilaginous repair tissue volume (eg, defect fill) compared with microfracture alone. Unfortunately, translational in vivo evidence suggesting improved histological structure or biomechanical function of the repair tissue is lacking. No translational in vivo studies have compared AMIC with ACI.[23]

Methodological Quality of the Studies

The CMS analysis revealed a suboptimal study design in the majority of recently published papers, especially regarding study size, type of study, and description of subject selection process. The restricted quality of the available studies indicates that the overall success of AMIC may potentially be biased due to prejudiced study design and outcome assessments. Interestingly, all 3 comparative trials comparing AMIC with microfracture have been performed with the involvement of companies distributing the AMIC membrane. In the future, it will be important to provide independent studies to avoid any perception of a bias.[35]

Is AMIC a Safe Procedure for Articular Cartilage Repair?

AMIC is a safe procedure. No serious adverse events related to the treatment were reported in any of the included studies that assessed treatment of chondral and osteochondral defects in knee, ankle, and hip joints. Two-thirds of the publications did not address the issue of complications. Specific complications resulting in a relatively low reoperation rate were mainly intralesional osteophytes, which are often related to the technique of microfracture.[18,41,44] Seldom, a conversion to total joint arthroplasty had to be performed (0.4%). Other unspecific complications mainly included joint stiffness (1.6%), joint catching (0.5%), effusion (0.2%) and others. It is possible that the term "joint stiffness" reflected arthrofibrosis—a complication reported for matrix-assisted ACI (6.4%),[5] but never within the context of AMIC.

Is AMIC Superior to Microfracture Alone at Long-term Follow-up?

Microfracture is a key part of the AMIC procedure. Its clinical success may depend on several factors such as defect size,[3] patient age,[2] depth of subchondral perforation,[10] dimensions of the microfracture awl,[45] and anatomic defect

location.[30] It is yet unknown how these factors affect the AMIC procedure, as no literature is available. Some combined surgical approaches reported clinical improvements,[57] but reported study designs—without control groups—render any assessment of the efficacy of each individual treatment difficult. Importantly, microfracture alone is performed arthroscopically and does not require arthrotomy. Only 2 randomized studies of AMIC versus microfracture are currently available for the knee joint. For cartilage defects with a mean defect size of 3.6 cm^2, AMIC improved clinical outcome scores significantly compared with microfracture at 5 years.[54] Unfortunately, although MRI was performed, no results of MOCART scoring were reported,[38] which may have provided more solid evidence on possible matrix-inducing properties of the type I/III collagen membrane. The fibrocartilaginous repair tissue revealed by the biopsies suggests an absence of cartilage regeneration. Yet, defect size is likely the most important parameter for the decision-making process in cartilage repair.[59] Chondral defects larger than 2.5 to 3.0 cm^2 represent an indication for ACI.[43] Therefore, the present data from the 2 studies involving the knee (mean defect size 3.6 cm^2) do not allow for a satisfactory answer as to whether AMIC shows superior clinical outcomes in long-term follow-up compared with microfracture (indicated for defects smaller than 2.5-3.0 cm^2).[49] Of note, a type I/III collagen membrane may be used in salvage cases covering large subchondral bone defects when the surgeon is aiming for biological reconstruction of the osteochondral unit after failed previous attempts at cartilage repair.[27] It is worthwhile to keep in mind that compared with ACI, AMIC entails only 1 operation.

Are Clinical Outcomes of AMIC Superior to Those of ACI?

For acetabular chondral lesions induced by FAI, the single-center retrospective analysis of a consecutive series of patients with the highest mean CMS of all evaluated studies found significantly improved clinical parameters in the AMIC group compared with microfracture.[21] The study by Mancini and Fontana[37] suggested that both arthroscopic ACI and AMIC resulted in similar clinical results. However, analysis of the study revealed a low CMS of 43, partly because the study was neither randomized nor multicenter and no structural outcomes such as MOCART score were reported. Also, the authors did not indicate whether concomitant procedures or previous surgery were performed, and it is unclear how many treated defects received additional fibrin glue fixation of the membrane. Finally, because the mHHS score was used, it is possible that some patients had osteoarthritis (OA), especially as radiological signs of moderate (Tönnis grade 2) OA were initially reported.[20] A recent study identified a significantly higher rate of conversion to total hip arthroplasty following hip arthroscopy in select patients with Tönnis grade 2 OA.[9] More clinical studies are needed to allow for a similar assessment of the possible superiority of AMIC for defects in other joints such as shoulder and ankle.

Which Specific Aspects Influence the Clinical Outcome of AMIC?

Greater improvements in clinical outcomes were reported for osteochondral compared with chondral defects in the knee,[32] although microfracture is usually not a first-line technique for osteochondral defects. For acetabular chondral defects, the data of the subgroup analysis comparing AMIC with microfracture suggest more pronounced effects of AMIC for defects 4 cm^2 or larger.[21] No other patient-specific aspects such as patient age, body mass index, and number of previous operations influenced the clinical outcomes. From a technical point of view, the fixation of the matrix in the defect is a crucial surgical step. It can be performed by suturing the matrix to the adjacent cartilage or by using subchondral fixation with glue, biodegradable pins,[39] or anchors.[22] In theory, fibrin glue may seal the penetrations of the subchondral bone plate induced by the microfractures, thereby possibly interfering with the subsequent migration of the MSCs into the defect. In cases of fibrin glue fixation,[17,26] an all-arthroscopic approach is technically feasible.[46] Fixation with sutures, pins, or anchors is often performed in conjunction with an arthrotomy (although all-arthroscopic techniques have been reported) and is considered to provide the best scaffold retention. Although membrane fixation requiring arthrotomy is surgically more hazardous and demanding, no study has yet revealed significant differences in clinical outcomes of AMIC related to the fixation technique.[1,54] Interestingly, for acetabular lesions sometimes no fixation is performed,[20,21,37] raising in theory the possibility of a loss of fixation of the implant and potential delamination.[19]

Strengths and Limitations

Strengths of this study include a comprehensive systematic review of the currently available evidence including high-quality studies by 2 independent reviewers. Limitations should also be noted, specifically the fact that only 3 studies compared AMIC with microfracture (2 in the knee and 1 in the hip) and only 1 study in the hip compared AMIC with matrix-assisted ACI. The CMS assessment demonstrated a suboptimal study design in the majority of published studies, underlining the continuous need for high-quality evidence. Finally, no study provided a statistical comparison between structural outcome parameters of chondrogenesis in cartilage defects. These facts make most of these studies difficult to interpret and to compare with established cartilage repair strategies. The definite answer to the key question whether AMIC is superior to microfracture or ACI therefore remains to be determined.

CONCLUSION

This systematic review reveals a paucity of high-quality, randomized controlled studies testing the AMIC technique versus established procedures such as microfracture or ACI for knee, ankle, and hip chondral defects. Evidence is therefore insufficient to recommend a possible range of

joint-specific defect sizes that may be treated with AMIC based on the limited and inadequate data from clinical trials. In the future, more nonbiased, high-powered, randomized controlled trials will provide better long-term clinical and quantitative structural evidence, thus helping to define possible indications for this technique.

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