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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Orthopedics is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central and Scopus.

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I-III Editorial Board

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NAME OF JOURNAL
World Journal of Orthopedics

ISSN
 ISSN 2218-5836 (online)

LAUNCH DATE
 November 18, 2010

FREQUENCY
 Monthly

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World Journal of Orthopedics
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 E-mail: editorialoffice@wjgnet.com
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PUBLISHER
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive,
 Suite 501, Pleasanton, CA 94588, USA
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 E-mail: bpgoffice@wjgnet.com
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<http://www.wjgnet.com>

PUBLICATION DATE
 July 18, 2017

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Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients

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Author contributions: Khan WS designed the research; Shaikh N, Seah MKT and Khan WS performed the research; Shaikh N, Seah MKT and Khan WS analyzed the data; Shaikh N and Seah MKT wrote the paper; all authors read and approved the final manuscript.

Conflict-of-interest statement: Each author certifies that he has no commercial associations that might pose a conflict of interest in connection with the submitted article.

Data sharing statement: None.

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Manuscript source: Invited manuscript

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Received: January 23, 2017

Peer-review started: January 29, 2017

First decision: May 11, 2017

Revised: May 28, 2017

Accepted: June 12, 2017

Article in press: June 13, 2017

Published online: July 18, 2017

Abstract

AIM

To systematically review the results of studies looking at autologous matrix-induced chondrogenesis (AMIC) in humans.

METHODS

A literature search was performed, adhering to the PRISMA guidelines, to review any studies using such techniques in humans. Our initial search retrieved 297 articles listed on MEDLINE, Google Scholar, CINHAL and EMBASE. From these studies, 15 studies meeting the eligibility criteria were selected and formed the basis of our systematic review.

RESULTS

The study designs, surgical techniques and outcome measures varied between the studies. Although all studies reported improvements in patient outcome measures, this was not necessarily correlated with magnetic resonance imaging findings. Although there were many additional procedures performed, when AMIC was performed in isolation, the results tended to peak at 24 mo before declining.

CONCLUSION

Although short-term studies suggest improved patient reported outcomes with a variety of scaffolds, surgical techniques and rehabilitation regimes, the literature remains equivocal on whether the defect size and location, and patient factors affect the outcome. Patient

benefit appears to be maintained in the short-to-medium term but more high level studies with extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Key words: Autologous matrix-induced chondrogenesis; Cartilage defects; Humans, PRISMA

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Core tip: Studies looking at autologous matrix-induced chondrogenesis (AMIC) in humans suggest improved patient reported outcomes in the short-to-medium term but there is significant variation in the scaffolds, surgical techniques and rehabilitation regimes used. The literature remains equivocal on whether the defect size and location, and patient factors affect the outcome. More high level studies with extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Shaikh N, Seah MKT, Khan WS. Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients. *World J Orthop* 2017; 8(7): 588-601 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/588.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.588>

INTRODUCTION

Cartilage defects have a limited capacity for repair^[1,2]. Untreated focal defects have the potential to progress to more generalised lesions and can cause significant morbidity. The frequent outcome for arthritis in large joints such as the knee is surgical intervention for joint replacement. This procedure is generally successful in older sedentary patients, but the limited lifetimes of prostheses make it much less desirable for younger and develop new strategies for the treatment of focal cartilage defects to prevent secondary osteoarthritis.

Various surgical procedures have been implemented to reduce pain, and postpone or prevent the need for joint replacement, while simultaneously withstanding the daily activities of the patient^[3]. These include the use of bone marrow stimulation techniques pioneered by Pridie by introducing the concept of subchondral drilling^[4,5]. This was further developed by Steadman who introduced the notion of microfracture^[6]. A range of chondrocyte implantation techniques have also developed including autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), mosaicplasty and osteochondral autologous transplantation (OATS)^[7-10].

In 2003 after funding issues were raised for two-

step procedures such as ACI and MACI partly in view of associated costs, a new one-step procedure was introduced for the repair of cartilage defects called autologous matrix-induced chondrogenesis (AMIC) that brings together microfracture with a collagen matrix scaffold^[11]. There is increasing interest in AMIC as it provides a cost-effective alternative to cell-based therapies for articular cartilage repair, and it is highly autologous in nature. Benthien and Behrens^[1] first described the AMIC procedure using an awl to perform perforations in the subchondral bone, and "partial autologous fibrin glue" (PAF) using commercially available fibrin glue to adhere Chondro-Gide[®] (Geistlich Biomaterials, Wolhausen, Switzerland) collagen membrane to the lesion. The TGF β component of fibrin may contribute to the chondrogenic differentiation of mesenchymal stem cells (MSCs)^[10]. Since then the procedure has been described with variations in the drilling technique, scaffold and fixation.

The results with AMIC in the literature have been variable. As there are limited studies on AMIC, variability in the type of scaffold used^[12-15], the surgical procedure^[1,13,15-17], defect size and location, and patient variability may all contribute to variable results. In addition, we are not aware of the longevity of these results. We performed a systematic review of the literature identifying studies looking at AMIC to determine their clinical outcome, and address these three questions: (1) does the type of scaffold, surgical technique or rehabilitation regime affect outcome? (2) does the defect size and location, and patient factors affect outcome? and (3) does the outcome change with time?

MATERIALS AND METHODS

A systematic review of the published literature was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines^[18]. This search was completed on November 30, 2016 using search databases MEDLINE, Google Scholar, Cumulative Index to Nursing and Allied Health Literature, AMED and EMBASE. No restrictions regarding publication date were applied during the literature search, due to the relatively new nature of AMIC and the limited number of related articles that have been published. Keywords used in the search include "autologous matrix-induced chondrogenesis" and "AMIC". The Cochrane library was also searched using the terms "autologous matrix-induced chondrogenesis" and "AMIC". Abstracts of the selected articles were reviewed to ensure they met the selection criteria, after which the full article was obtained. The bibliographies and in-text references of the retrieved articles were searched for any articles that may have been missed during the initial search. Unpublished or grey literature was identified using databases including System for Information on Grey Literature in Europe, the National

Technical Information Service, the National Research Register (United Kingdom), UKCRN Portfolio Database, the National Technical Information Service, the British Library's Integrated Catalogue, and Current Controlled Trials database. Published and unpublished material including university theses and dissertations, and conference proceedings in the English literature were also reviewed.

The inclusion criteria were clinical studies in English language looking at outcomes after AMIC in partial- and full-thickness focal chondral or osteochondral defects (ICRS grade III or IV) of any joint. Studies with a level of evidence I-IV as described by the Oxford Centre for Evidence-based Medicine^[19] were included. Studies not meeting these criteria, single-patient case studies, techniques, comments, letters, editorials, protocols and guidelines were excluded. Animal and cadaveric studies were also excluded.

The titles and abstracts of all citations were reviewed by the three authors (Shaikh N, Seah MKT and Khan WS). Full manuscripts of citations adhering to the inclusion criteria and those that were uncertain were downloaded. Reference lists of all full manuscripts and applicable review articles were reviewed to identify any further articles omitted from the initial search. The same investigators then reviewed all full manuscripts against the inclusion criteria and any disagreement on eligibility was resolved by discussion. The corresponding author of the paper was contacted if any queries arose. They were also consulted as to any additional citations that may address the research question.

Data was extracted from papers that satisfied the eligibility criteria. The variables that were determined for each study were study type, treatment period, study size, gender, mean age, patients lost to follow-up, mean and range of follow-up, joint involved, size, grade and location of lesion, inclusion and exclusion criteria, source of funding, surgical technique, previous and associated surgeries, rehabilitation and outcome scores. The extracted data was entered onto Microsoft Excel (Microsoft Corporation, Washington, DC) by one investigator (Shaikh N), and re-evaluated and verified by the other authors (Seah MKT and Khan WS). The investigators were blinded to the source or authors of the identified papers. Although the systematic review protocol was approved by the host institution, the systematic review protocol was not formally registered in a registry. A systematic review was performed rather than a meta-analysis in view of the lack of randomised controlled trials and consistent outcome measures, where the results could be combined to allow statistical analyses.

Study quality assessment

The Coleman Methodology Score (CMS)^[20] was used to evaluate the quality of the studies and to determine if the outcomes and claims made in particular studies

should be given more weighting than others. The ratings were also used as a guide to assess the level of confidence from which conclusions could be drawn from a particular study. CMS consists of two parts; Part A that focuses on the design of the study and Part B that relates to the study outcomes. This instrument uses a scaling system, in which the studies are assessed using 10 criteria. Part A has a maximum total score of 65, while Part B has a maximum total score of 35, giving a total score of 100. The total score can be graded as being excellent (85-100 points), good (70-84 points), fair (55-69 points) and poor (< 55 points). A higher total score suggests that the study has an efficient design and is better at avoiding the effects of chance, various biases and confounding factors. The categories used in the CMS were formed on the basis of the Consolidated Standards of Reporting Trials statement for randomized controlled trials^[21].

RESULTS

The results of the search using the databases retrieved 297 articles. Twenty-six articles were reviewed after excluding animal and pre-clinical studies, single-patient case reports, literature reviews and articles where the original text was in a language other than English. Of the 26 articles obtained, 10 were excluded as they represented level V evidence, review studies or technical notes, resulting in a total of 16 articles that were included in this systematic review (Figure 1)^[3,13,15-17,22-33]. Of the 16 included articles, 13 studies were prospectively conducted, 2 were retrospective, and only 1 was a randomized control trial.

There were more males than females included in the studies, with a ratio of approximately 2:1. The mean age was 36.2 years (range 15-50 years) and the mean follow-up period was 30 mo (range 6-62 mo). Ten of the 16 studies focussed on the knee, 3 on the ankle, and 3 on the hip (Table 1). Some of the studies mentioned sources of funding, but none that would trigger any concerns about conflict of interests or bias. A variety of treatment algorithms were used including different drilling techniques, scaffold used, method of fixation, associated surgery and the rehabilitation protocol (Table 2).

All of the studies adopted at least one form of established patient-reported outcome measure and 9 of the 16 studies obtained patient Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) scores (Tables 3 and 4). For the 10 studies looking at the knee, all reported more than one clinical outcome measure. Five used the Visual Analogue Scale (VAS), 4 used the Lysholm score and the Knee injury and Osteoarthritis Outcome Score (KOOS), 3 used the International Knee Documentation Committee (IKDC) score, 2 used the International Cartilage Repair Society (ICRS) and the Cincinnati score, and 1 used the Tegner score and Kujala patellofemoral score.

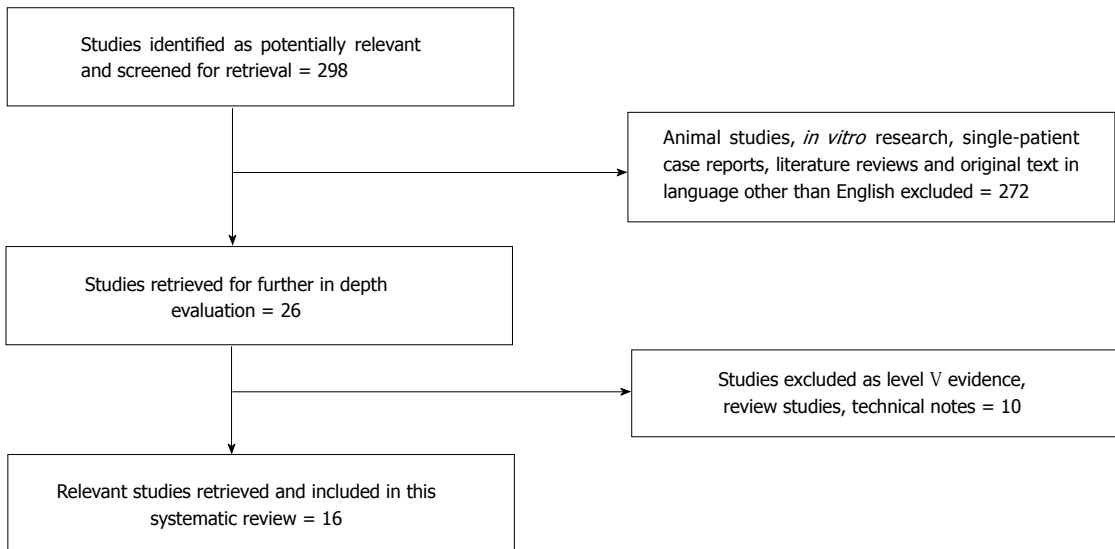


Figure 1 Illustration of the selection process for articles in this systematic review.

The three studies looking at the ankle joint used the American Orthopaedic Foot and Ankle Society (AOFAS) score and the VAS. One study also reported the Foot Function Index (FFI). Two of the hip studies reported the modified Harris Hip Score (mHHS). Four knee, four ankle and one hip studies also reported on MOCART scores. Although positive patient-reported outcomes were observed in all studies, MOCART scores did not always correlate with the patient-reported outcomes.

Kusano *et al.*^[22] found significant improvements in the IKDC and Lysholm scores, but the MOCART scores did not correlate with the positive clinical outcomes. The majority of patients displayed incomplete defect repair, damaged repair tissue, and inhomogeneous repair tissue structure, as well as subchondral lamina and subchondral bone that were not intact. The randomized control trial by Anders *et al.*^[3] assessed differences between a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. In all three groups, positive patient outcomes and pain levels were observed at follow-up, with no significant differences between the groups. In assessing the magnetic resonance imaging (MRI) outcomes of patients in this study, results showed good defect filling in most patients, however homogenous repair tissue was only seen in 50% of the patients treated using the AMIC techniques, compared to 100% of the patients treated using traditional microfracture. Additionally, surface regeneration and integration of the lesion with the cartilage proved to be marginally inferior in patients that were treated using AMIC. The finding that MRI scores do not always correspond with patient-assessed outcomes is consistent with those observed in other studies. Dhollander *et al.*^[29] found favourable clinical outcome scores in patients undergoing AMIC at the patellofemoral joint but the radiological findings did not support these outcomes. All 10 patients

had subchondral lamina changes on MRI and 3 had osteophytes within 24 mo.

Does the type of scaffold, surgical technique or rehabilitation regime affect outcome?

There are three commercially available biodegradable membrane scaffolds that fill in the lesions until they are absorbed and replaced by repair tissue (Table 2). The three scaffolds are Chondro-Gide[®], Chondrotissue[®] (BioTissue, Zurich, Switzerland) and Hyalofast[™] (Fidia Advanced Biopolymers, Padua, Italy). Chondro-Gide[®] is a porcine-based membrane that is the original and most popular scaffold used in AMIC. This protein-based matrix has a bi-layer structure composed primarily of type I/III collagen. In cases where the AMIC Plus technique^[16] was implemented, a Platelet-rich plasma (PRP) gel (GPS[®] III System Advantages, Biomet) was applied to the surface of the lesion prior to the application of the membrane. Chondrotissue[®] is "sponge-like" matrix composed of polyglycolic acid treated with hyaluronan^[12,13]. In cases where Chondrotissue[®] was used, PAF was substituted with biodegradable pins^[13]. The Hyalofast[™] membrane is a partially-synthetic by-product of hyaluronic acid composed of an unstructured amalgamation of fibres. On degradation it releases hyaluronic acid into the defect site that may encourage chondrogenic differentiation of bone marrow-derived MSCs^[14]. Prior to commencing the AMIC procedure, bone marrow is aspirated from the iliac crest, and processed to obtain bone-marrow derived MSCs. This is used with autologous PRP obtained from the blood sample, and together the Hyalofast[™] membrane is immersed in this solution prior to being applied onto defect^[15]. Buda *et al.*^[15] performed the AMIC procedure on 20 patients using Hyalofast[™] membrane, and the improvements in the IKDC scores were greater than those seen with Chondro-Gide[®] membrane. The mean

Table 1 Study demographics, lesion location and grade, inclusion and exclusion criteria, and funding sources

Ref.	Treatment period	Patient numbers	Mean age (yr)	Mean follow-up in months (range)	Joint	Defect location and type	Grade of lesion	Lesion dimensions (cm ²)	Inclusions	Exclusions	Source of funding
Shetty <i>et al</i> ^[34]	4 yr	30				MFC, LFC, trochlea, patella	Grade III/IV	2-8		Malalignment of the knee exceeding 5° of valgus or varus. Generalized osteoarthritic changes in the knee	
Buda <i>et al</i> ^[15]	Apr 2006-May 2007	20 (12M, 8F)	15-50	29	Knees		Grade III/IV	Not specified		Diffuse arthritis, general medical conditions (<i>e.g.</i> , diabetes, rheumatoid arthritis etc.), haematological disorders and infections	None
Gille <i>et al</i> ^[26]	2003-2005	27 (16M, 11F)	39	37 (24-62)	Knees	Medial femoral condyle 7, lateral femoral condyle 3, patella 9, trochlea 2, femoral condyle and patella 6	Grade IV	> 1	Clinical symptomatic chondral lesions at femoral condyle, patella or trochlea	Advanced osteoarthritis, rheumatic disease, total meniscectomy, BMI > 35, deviation of mechanical axis to the affected compartment	Not specified
Dhollander <i>et al</i> ^[16]	Jan 2008-Apr 2008	5 (3M, 2F)	18-50	24 (12-24)	Knees	Patella	Grade III/IV	2 (range 1-3)	Symptomatic focal patella cartilage defects	Untreatable tibiofemoral or patellofemoral malalignment, diffuse osteoarthritis, major meniscal deficiency or other general medical conditions	Not specified
Dhollander <i>et al</i> ^[13]	2008-2009	5 (4M, 1F)	29.8	24	Knees	Right 2 (40%), left 3 (60%) medial femoral condyle (2), lateral femoral condyle (2), trochlea (1)	Grade III/IV	Median 2.3, range 1.5-5	16-40 yr, single symptomatic focal cartilage defect on femoral condyles or patellofemoral joint	Untreated tibiofemoral or patellofemoral malalignment or instability, diffuse osteoarthritis, bipolar "kissing" lesions, major meniscal deficiency and other general medical conditions	Not specified
Kusano <i>et al</i> ^[22]	Aug 2003-Jul 2006	40 (23M, 17F)	35.6	28.8 (13-51)	Knees	Full thickness chondral defect in patella (20), femoral condyle (9), osteochondral defect in femoral condyle (11)	Grade III/IV	3.87		Defects in other locations, age > 50 yr, skeletally immature	Not specified

Leunig <i>et al</i> ^[23]	Mar 2009-Dec 2010	6 (5M, 1F)	22.7	Not specified (12-30)	Hips	Femoral head 5, acetabular 1 chondral 1, osteochondral 5	Grade III/IV	> 2	Full thickness chondral lesions > 2 cm ² or osteochondral lesions > 1 cm ² with defects in weight-bearing areas of acetabulum or femoral head, irreparable by osteotomy in age < 35 yr	Patients unwilling or unable to comply with post-operative rehabilitation protocols. Systematic inflammatory arthritis, advanced arthritis involving both femur and acetabulum, or age > 35 yr	Not specified
Pascarella <i>et al</i> ^[24]	2006-2008	19 (12M, 7F)		12-36	Knees	Right knee: Femoral condyle (medial 34%, lateral 14%), patella (9%) Left knee: Femoral condyle (medial 29%, lateral 14%)	Grade III/IV	3.6	Age 18-50 yr with single lesion	Osteoarthritis, axial deviations, ligamentous injuries, complete meniscal resection, allergy to collagen membrane components	Not specified
Anders <i>et al</i> ^[21]	Jan 2004-Mar 2010	38 (Not specified)	37	19 (6-24)	Knees		Grade III/IV	3.4	Age 18-50 yr, 1-2 lesions	> 2 defects, corresponding defects, bilateral defects, signs of osteoarthritis, other general diseases, history of complete meniscectomy, mosaicplasty, treatment with cartilage specific medication, chondroplasia patallae or patellar dysplasia	None
Gille <i>et al</i> ^[28]	Not specified	57 (38M, 19F)	37.3	24	Knees	Medial condyle (32), lateral condyle (6), trochlea (4), patella (15) Grouping based on lesion size: Group A 0-3 cm ² , Group B 3-6 cm ² , Group C 6-9 cm ²	Grade III (35), Grade IV (37)	3.4 (1-12)	Age 17-61 yr	Rheumatic disease, total meniscectomy, and revision surgery	Not specified
Valderrabano <i>et al</i> ^[17]		26 (18M, 8F)	33	31 (25-54)	Ankles	Osteochondral lesions of talus		1.68	First time osteochondral lesion or failure of previous lesion	Age > 55 yr, open ankle physis	Not specified
Wiewiorski <i>et al</i> ^[25]	2008-2010	23 (16M, 7F)	34	23 (11-49)	Ankles (talus)	Osteochondral lesions of talus	Osteochondral	1.49	Single lesion with history of ankle trauma		Not specified

Dhollander <i>et al</i> ^[29]	April 2009-May 2011	10 (8M, 2F)	37.2 ± 7.1	24	Knee	Patella (8), trochlea (2)	Grade III/IV	4.2 ± 1.9	Patients aged 18-50 yr with a focal patellofemoral defect and clinical symptoms (pain, swelling, locking, giving way)	Untreatable tibio-femoral or patellofemoral mal-alignment or instability, diffuse osteoarthritis or bipolar "kissing" lesions, major meniscal deficiency and other general medical conditions (diabetes, rheumatoid arthritis)	Not specified
Mancini <i>et al</i> ^[30]	November 2004-June 2007	31	36.4 ± 10.3	60	Hip	Acetabular chondral defects	Grade III/IV	2-4	Patients 18-50 yr of age with acetabular chondral lesions with radiological Tönnis degree < 2 followed up to 5 yr	Concomitant chondral kissing lesion, systemic rheumatoid diseases, dysplasia, femoral neck axial deviations, coxa profunda, protrusio acetabuli	Not specified
Fontana <i>et al</i> ^[31]	November 2004-March 2011	55	39.1 (18 to 55)	36-60	Hip	Acetabular ± femoral head chondral defects	Grade III/IV	2-8	Patients 18-55 years of age with acetabular ± femoral head chondral lesions with radiological Tönnis degree < 2 followed up for 3-5 yr	Rheumatoid arthritis, dysplasia, axial deviation of the femoral neck, coxa profunda, protrusio acetabuli	Not specified but Girolamo is a paid consultant for Geistlich
Kubosch <i>et al</i> ^[32]	Not specified	17	38.8 ± 15.7	39.5 ± 18.4	Ankle	Osteo-chondral lesions of talus	Grade III/IV	2.4 ± 1.6	First-time diagnosis or failure of a previous operative treatment	Arthritis of the ankle joint, kissing lesions and rheumatoid arthritis	Not specified

BMI: Body mass index.

KOOS score at follow-up in this study were significantly greater than those reported by Dhollander *et al*^[16,29] using Chondro-Gide® and in Dhollander *et al*^[13] using Chondrotissue. The clinical outcomes achieved in Buda *et al*^[15]'s study were partly supported by the MOCART scores, with a majority of patients displaying complete defect repair, complete integration to surrounding cartilage, intact repair tissue surface, and iso-intense signal intensity, while other MRI measures showed poor results despite positive patient-assessed outcomes. The remainder of the studies in this review used Chondro-Gide® and resulted in patient outcomes that were posi-

tive and comparable.

Several drilling techniques were adopted in the studies. In 6 of the 16 studies, an awl was used to perforate the subchondral surface of the bone as originally described^[1]. Seven studies substituted an awl with a microdrill, with or without Kirchner wires^[23,24]. Pascarella^[24] carried out a slightly modified AMIC procedure with the intention of increasing the number of MSCs to produce healthy regenerative cartilage. Perforations were performed rather than microfractures, and the covering of the focus of the lesion with a biological collagen patch enriched with bone marrow

Table 2 Treatment algorithms

Ref.	Drilling technique	Scaffold/fixation	Associated surgery	Joint	Rehab
Buda <i>et al</i> ^[15]	No drilling	Hyalofast + PRP	3 osteotomy	Knees	NWB 4 wk, run 6 mo, RTS 12 mo
Gille <i>et al</i> ^[26]	Awl/sharp cannula	ChondroGide Fibrin glue	2 realignments, 1 capsular shift	Knees	Immobilization 1 wk, passive motion 6 wk, NWB 6 wk
Dhollander <i>et al</i> ^[16]	Microdrill	ChondroGide + PRP Sutures	3 osteotomy + 1 medial patello-femoral ligament reconstruction	Knees	NWB 2 wk, brace 0-90 for 4 wk, full ROM at 8 wk, Low impact sports 12 mo
Dhollander <i>et al</i> ^[13]	Microdrill	Chondrotissue Pin	1 osteotomy	Knees	NWB 2 wk, 0-90° 4 wk, full range 8 wk, RTS 12 mo
Kusano <i>et al</i> ^[22]	Awl	ChondroGide Suture/fibrin glue	28 osteotomy	Knees	PWB 6 wk, 0-60 4wk
Leunig <i>et al</i> ^[23]	Kirchner wire	ChondroGide, fibrin glue	3 osteoplasty, 2 femoral neck lengthening, drilling of acetabular defects	Hips	PWB 6-8 wk, passive motion 6-8 h for 6-8 wk
Pascarella <i>et al</i> ^[24]	Kirchner wire	ChondroGide Fibrin glue		Knees	
Anders <i>et al</i> ^[3]	Awl	ChondroGide Suture/fibrin glue		Knees	PWB and lymphatic draining massage 3-6 wk, FWB at 4-6 mo, RTS 3-18 mo
Gille <i>et al</i> ^[28]	Awl	ChondroGide Fibrin glue	2 patella realignments, 3 corrective osteotomies, 6 partial menisectomies, 1 ACL reconstruction	Knees	
Valderrabano <i>et al</i> ^[17]	Microdrill	ChondroGide Fibrin glue	16 osteotomy	Ankles	PWB, ROM of < 200 passive motion machine, lymphatic drainage massage 6wks, FWB 6-12 wk, Light sports 12 wk, RTS 5-6 mo
Wiewiorski <i>et al</i> ^[25]	Microdrill	ChondroGide Fibrin glue		Ankles (talus)	PWB and lymphatic draining massage 6 wk, FWB 12 wk
Dhollander <i>et al</i> ^[29]	Slow speed 1.2 mm diameter	ChondroGide Vicryl 6/0	No	Knees (Patellofemoral joint)	NWB for 2 wk, FWB at 10 wk, full range of motion at 8 wk, low impact sports 12 mo
Mancini <i>et al</i> ^[30]	Awl/sharp cannula	ChondroGide Fibrin glue	All patients had cam-type and/or pincer-type impingement, and underwent arthroscopic femoral head-neck resection arthroplasty and/or arthroscopic acetabular rim trimming and labral reattachment to the acetabular rim with suture anchors	Hips	PWB (30% of body weight) for 4 wk, impact sports 3 mo, complete RTS 6 mo
Fontana <i>et al</i> ^[31]	Awl/sharp cannula	ChondroGide Fibrin glue	All patients had cam-type and/or pincer-type impingement, and underwent arthroscopic femoral head-neck resection arthroplasty and/or arthroscopic acetabular rim trimming and labral reattachment to the acetabular rim with suture anchors	Hips	PWB for 7 wk, light sporting activities 4 wk, low impact sports 6 mo, complete RTS 12 mo
Kubosch <i>et al</i> ^[32]	Not specified	ChondroGide Fibrin glue	All patients also underwent autologous cancellous bone grafting to the site	Ankles (talus)	Ankle immobilisation for 2 wk, PWB for 6 wk
Shetty <i>et al</i> ^[34]	Microdrill	Tiseel Coltrix (atelocollagen)	-	Knees	PWB for 6 wk, gradual increase to FWB by next 6 wk

PRP: Platelet-rich plasma; ACL: Anterior cruciate ligament; PWB: Partial weight bearing; NWB: Non-weight bearing; FWB: Full weight bearing; ROM: Range of motion; RTS: Return to sport.

Table 3 Summary of patient outcome scores of the 16 reviewed studies

Ref.	Sub-groupings (Where Applicable)	Follow-up (mo)	Outcomes														
			KOOS		IKDC		VAS		ICRS		Cincinnati		Lysholm		Other		
			Pre-surgery	At follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	
Buda <i>et al</i> ^[15]		29 ± 4.1	47.1 ± 14.9	93.3 ± 6.8	32.9 ± 14.2	90.4 ± 9.2			31 ± 15	37 ± 4	46 ± 18	37 ± 9	36 ± 21				
Gille <i>et al</i> ^[26]		48															
Dhollander <i>et al</i> ^[16]		24	41.6	71.4													
Dhollander <i>et al</i> ^[23]		24	37.6 ± 16.7	73.1 ± 25													
Kusano <i>et al</i> ^[22]	ocF	28.8 ± 1.5	44 ± 25	88 ± 9									50 ± 25	94 ± 8			
	cP	28.8 ± 1.5	51 ± 25	74 ± 17									58 ± 17	85 ± 13			
	cF	28.8 ± 1.5	45 ± 26	68 ± 14									56 ± 25	76 ± 18			
Leunig <i>et al</i> ^[29]		Not specified															
Pascarella <i>et al</i> ^[34]		24	30	83									54	98			
Anders <i>et al</i> ^[3]	MFx	24						54 ± 21	19 ± 17	40 ± 9	83 ± 8						
	Sutured AMIC	24						46 ± 19	14 ± 13	43 ± 16	88 ± 9						
	Glued AMIC	24						48 ± 20	16 ± 13	48 ± 15	85 ± 18						
Gille <i>et al</i> ^[28]		24						7 ± 1.8	2 ± 2.1				50.1 ± 19.6	85.2 ± 18.4			
Valderrabano <i>et al</i> ^[17]		31						5 ± 2	2 ± 2								
Wiewiorski <i>et al</i> ^[25]		23						4.8 ± 1.6	1.3 ± 2								
Dhollander <i>et al</i> ^[20]		24	44.5 ± 17.5	65.0 ± 23.3				73.9 ±	39.4 ±								
	Defect < 4 cm ²	60						20.8	28.8								
	Defect > 4 cm ²	60															
Kubosch <i>et al</i> ^[32]		39.5 ± 18.4						7.8 ± 2.1	3.2 ± 2.4								
Shetty <i>et al</i> ^[34]		48	64.7	88.2	39	78.6							50.8	80.4			

KOOS: Knee injury and Osteoarthritis Outcome Score; IKDC: International Knee Documentation Committee; VAS: Visual Analogue Scale; AOFAS: American Orthopaedic Foot and Ankle Society; ICRS: International Cartilage Repair Society; mHHS: Modified Harris Hip Score; FFI: Foot Function Index; MOCART: Magnetic resonance Observation of Cartilage Repair Tissue.

blood drawn through the knee itself. The aim of the study was simply to show that the modified AMIC procedure was a viable alternative to current surgical practices. The IKDC and Lysholm scores showed a similar trend to that observed by Kusano *et al*^[22], with the mean IKDC score increasing from 30 to 83 in 24 mo, and the mean Lysholm score increasing from 54 to 98. MRI scores showed a significant reduction of the defect area, although detailed MRI evaluations were not available. Similarly Valderrabano^[17] introduced a modified AMIC procedure that involved the addition of spongiosa bone harvested from the iliac crest to increase the number of MSCs being recruited. This graft is inserted into the lesion and the membrane placed on top. They reported significant improvement in the mean AOFAS scores from 62 to 89 for 26

Table 4 Summary of detailed magnetic resonance imaging evaluation results if provided from studies that reported Magnetic resonance Observation of Cartilage Repair Tissue scores

Scoring measure	Outcome	Number and percentage of patients that achieved a particular result for each category of the MOCART scoring system															
		Buda <i>et al.</i> ^[15]	Dhollander <i>et al.</i> ^[16]	Dhollander <i>et al.</i> ^[13]	Kusano <i>et al.</i> ^[22]	Leunig <i>et al.</i> ^[23]	Valderrabano <i>et al.</i> ^[17]	Wiewiorski <i>et al.</i> ^[25]	Dhollander <i>et al.</i> ^[29]								
		No. of Pts.	% of Pts.	No. of Pts.	% of Pts.	No. of Pts.	% of Pts.	No. of Pts.	% of Pts.	No. of Pts.	% of Pts.	No. of Pts.	% of Pts.				
Degree of defect repair	Complete	14	70%	0	0%	1	20%	3	19%	4	100%	9	35%	8	35%	2	20%
	Hypertrophy	4	20%	2	40%	2	40%	3	19%	0	0%	13	50%	12	52%	2	20%
	Incomplete	2	10%	3	60%	2	40%	10	63%	0	0%	4	15%	3	13%	6	60%
Integration to the Surrounding Cartilage	Complete	16	80%	4	80%	1	20%	8	50%	4	100%	9	35%	8	35%	4	40%
	Incomplete	2	10%	0	0%	4	80%	4	25%	0	0%	9	35%	0	0%	2	20%
	Defect visible	2	10%	1	20%	0	0%	4	25%	0	0%	8	31%	15	65%	4	40%
Surface of the Repaired tissue	Intact	14	70%	0	0%	1	20%	2	13%	3	75%	17	65%	15	65%	3	30%
	Damaged	6	30%	5	100%	4	80%	14	88%	1	25%	9	35%	8	35%	7	70%
Structure of the Repaired tissue	Homogeneous	6	30%	0	0%	0	0%	0	0%	1	25%	7	27%	6	26%	4	40%
	Inhomogeneous	14	70%	5	100%	5	100%	16	100%	3	75%	19	73%	17	74%	6	60%
Signal Intensity	Isointense	13	65%	0	0%	2	40%	1	6%	2	50%	4	15%	3	13%	1	10%
	Hyperintense	7	35%	5	100%	2	40%	15	94%	1	25%	18	69%	17	74%	6	60%
	Hypointense	0	0%	0	0%	1	20%	0	0%	1	25%	4	15%	3	13%	3	30%
DIPSE	Intact	6	30%	0	0%	0	0%	3	19%	1	25%	9	35%	8	35%	0	0%
	Not intact	14	70%	5	100%	5	100%	13	81%	3	75%	17	65%	15	65%	10	100%
Subchondral bone	Intact	6	30%	0	0%	1	20%	4	25%	2	50%	3	12%	3	13%	6	60%
	Not intact	14	70%	5	100%	4	80%	12	75%	2	50%	23	88%	20	87%	4	40%
Adhesions	No	20	100%	5	100%	5	100%	15	94%	3	75%	26	100%	23	100%	10	100%
	Yes	0	0%	0	0%	0	0%	1	6%	1	25%	0	0%	0	0%	0	0%
Effusion	No	17	85%	5	100%	3	60%	6	38%	4	100%	25	96%	22	96%	7	70%
	Yes	3	15%	0	0%	2	40%	10	63%	0	0%	1	4%	1	4%	3	30%

patients. MRI findings however showed that only 35% of participants displayed complete filling of the defect, and less than half of the participants returned to their previous level of activity. There were also slight variations depending on the region that needed to be operated upon. The study by Anders *et al.*^[3] assessed differences in efficacy and safety between a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. Although the sutured AMIC group showed the greatest improvement in mean Cincinnati scores, there were no significant differences between the groups.

In more than half of the studies, additional surgery was required on at least one subject in the study. The most common additional procedure required was osteotomy and bony realignment. All patients who underwent AMIC at the hip joint underwent additional surgery, mostly for impingement. In the study carried out by Kusano *et al.*^[22] looking at the knee joint, patients treated with AMIC alone were compared with patients who had an associated procedure such as an osteotomy. No significant differences in outcomes were noted.

Post-operative rehabilitation regimes varied for the various studies, and were influenced by the location and extent of the lesion. Three studies^[3,17,25] included lymphatic drainage massage as part of their rehabilitation process. The post-operative regime generally involved a period of reduced weight-bearing that may include immobilisation of the joint, followed by a periodic increase in weight-bearing and range of motion. Full-weight bearing commenced from 6 wk to 6 mo. Return to sports periods also lacked consistency, with subjects being able to return to sports after as little as 12 wk^[17], and as much as 18 mo^[3].

Does the defect size and location, and patient factors affect outcome?

For all of the studies investigated, the AMIC procedure was carried out on subjects that had either grade III or grade IV type lesions, although the three ankle-based

Table 5 Coleman methodology scores for the 15 reviewed studies reporting on autologous matrix-induced chondrogenesis

Ref.	Coleman methodology score															Total, max = 100	
	Part A, maximum = 65						Part B, maximum = 35										
	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9		
Buda <i>et al</i> ^[15]	0	4	0	10	10	5	2	2	3	3	5	4	3	3	5	5	64
Gille <i>et al</i> ^[26]	4	4	7	10	10	5	2	2	3	3	5	4	3	3	5	5	75
Dhollander <i>et al</i> ^[16]	0	4	10	10	10	5	2	2	3	3	5	0	3	0	5	5	67
Dhollander <i>et al</i> ^[13]	0	4	10	10	10	5	2	2	3	3	5	4	3	3	5	5	74
Kusano <i>et al</i> ^[22]	4	4	10	0	10	5	2	2	3	3	5	0	3	3	5	5	64
Leunig <i>et al</i> ^[23]	0	4	10	0	10	5	2	2	3	3	5	4	3	0	5	0	56
Pascarella <i>et al</i> ^[24]	0	4	10	10	0	5	0	2	3	0	5	0	3	0	5	5	52
Anders <i>et al</i> ^[3]	4	0	0	10	10	5	2	2	3	3	5	0	3	0	5	0	52
Gille <i>et al</i> ^[28]	7	4	10	0	0	0	2	2	3	3	5	0	3	0	5	5	49
Valderrabano <i>et al</i> ^[17]	0	4	10	10	10	5	2	2	3	3	5	0	3	0	5	5	67
Wiewiorski <i>et al</i> ^[25]	0	4	10	10	10	0	2	2	3	0	0	0	3	3	5	5	57
Dhollander <i>et al</i> ^[29]	0	4	10	0	10	5	2	2	3	3	5	0	3	3	5	5	60
Mancini <i>et al</i> ^[30]	4	7	0	10	5	5	2	2	3	0	5	0	3	3	5	5	59
Fontana <i>et al</i> ^[31]	7	7	0	10	5	5	2	2	3	0	5	0	3	3	5	5	62
Kubosch <i>et al</i> ^[32]	0	7	10	0	0	5	2	2	3	3	5	0	3	3	5	5	53
Shetty <i>et al</i> ^[34]	4	7	10	0	0	5	2	2	3	3	5	0	3	3	5	0	52

studies^[17,25] did not specify the grade of lesions. The studies focussed on both osteochondral and chondral defects of the joints. Although the lesions varied from 1-8 cm², the mean lesion size for all studies ranged from 1.5-3.6 cm². In the ankle based studies all AMIC procedures were conducted on the talus, and a majority of the knee based studies involved the AMIC procedure being carried out on the femoral condyle.

Kusano *et al*^[22] compared 40 defects; 11 were Osteochondral Femoral Condyle lesions (ocF), 20 were Chondral Patella lesions (cP), and nine were Chondral Femoral Condyle lesions (cF). The ocF group had the lowest mean age at 25.9, while the mean age for the other groups was just below 40. Only 36% of patients in the ocF group had an osteotomy compared with 90% in the cP group and 67% in the cF group. The cF group had a significantly smaller mean lesion size (2.3 cm²), compared with 4.2 and 4.4 cm² in the other groups. The patient outcome scores were consistent across the groups. Although the cP group reported the highest mean pre-operative scores, the ocF group showed the greatest improvement at follow-up, and the cF group showed the least improvement. As there were inconsistencies between the three groups relating to age and size of lesion, it is difficult to draw a definitive conclusion from these results. Gille *et al*^[26] followed up patients for 48 mo and failed to identify any significant effect of lesion size on Patient outcome scores. They did however find that outcomes were better for femoral condyle defects than patella defects, and the two patients who had cartilage defects greater than 8 cm² did not benefit from the procedure. Fontana *et al*^[31] compared AMIC with microfracture at the hip joint in patients undergoing impingement surgery, and only found a better five-year clinical outcome for the AMIC group for lesions greater than 4 cm².

Interestingly Fontana *et al*^[31] only found the five-

year results to be better for the AMIC group in males, and not females. Looking at the remaining studies, males generally reported higher outcome scores but showed similar levels of improvement to females after treatment. In the study carried out by Kusano *et al*^[22], the results suggested that younger patients generally experience greater improvements than older patients. Gille *et al*^[26] reported on patient outcome scores at 48 months, and failed to identify any significant effect of age, weight, gender, and previous surgery on patient outcome, but younger patients did generally display better recovery rates than older patients.

Does the outcome change with time?

Mancini *et al*^[30] and Fontana *et al*^[31] reported five-year follow-up in patients undergoing AMIC at the hip joint but all patients underwent additional impingement surgery. The authors report improved outcome scores that were achieved at six months and generally maintained till final follow-up at five-years. Gille *et al*^[26] reported on ICRS, Cincinnati, and Lysholm patient-assessed scores at 24, 36, and 48 mo for patients undergoing AMIC at the knee joint with less than 10% of patients undergoing additional procedures. Patient recovery tended to peak at 24 mo before declining. The mean Cincinnati score peaked at 74 at 24 mo, and steadily declined to 62 (36 mo) and 37 (48 mo). For all scoring systems, the patient outcomes deteriorated more rapidly once they passed the 36 mo follow-up. The randomized control trial by Anders *et al*^[3] compared a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. None of the patients underwent any additional procedures. In all three groups, improvements in pain scores and patient outcomes, including Cincinnati scores, were observed at both 12 and 24 mo follow-up. Between 12 and 24 mo follow-up, 12 patients showed further

Table 6 Coleman methodology scores - mean, range and standard deviation for each section

Section score (maximum)	Mean	Range	SD
Part A (65)			
Study size	2.1	0-7	2.6
Minimum follow-up	4.5	0-7	1.7
Number of different surgical treatment included	7.3	0-10	4.3
Study design	6.3	0-10	4.8
Description of surgical technique	6.9	0-10	4.3
Post-Op management described	4.4	0-5	1.7
Total part A	31.4	21-40	5.7
Part B (35)			
Outcome measures clearly defined	1.9	0-2	0.5
Timing of outcome clearly stated	2	2	0
Use of reliable outcome criteria	3	3	0
General health measure inc.	2.2	0-3	1.3
Subjects recruited	4.7	0-5	1.2
Inv. independent of surgeon	1	0-4	1.7
Written assessment	3	3	0
Completion of assessment by patients with minimal investigator assistance	1.9	0-3	1.5
Selection criteria reported and unbiased	5	5	0
Recruitment rate reported	4.1	0-5	2
Total part B	28.9	23-35	3.9
Total, maximum = 100	60.2	49-75	7.7

improvement in Cincinnati scores, 12 showed little or no change, and 3 showed a decline.

Methodological quality assessment

CMS was used to assess the methodological quality of the studies carried out using the AMIC procedure (Tables 5 and 6). The mean CMS and standard deviation (SD) achieved was 60.7 ± 7.9 (range 49-75) out of 100. The mean CMS and standard deviation (SD) achieved in Part A was 31.8 ± 5.9 , and in Part B was 28.9 ± 4.1 .

DISCUSSION

AMIC enables the transplantation of a scaffold with MSCs in one step, avoiding the need for laboratory cell number expansion and a second procedure^[26]. In our review, 15 studies between 2003 and 2015 that used AMIC for the repair of articular cartilage defects in patients were systematically reviewed. AMIC is still a relatively new procedure and more mid-term and long-term outcomes are awaited. The mean CMS suggesting that the overall quality of the studies was fair. Studies scored poorly for number of patients, length of follow-up, study design and independence of the investigator and the surgeon. For Part A, the overall mean CMS was 31.8 out of 65 points (49%), whereas for Part B the overall mean CMS was 28.9 out of 35 (72%). This indicates that overall, the studies were more competent in defining their outcome criteria and procedures, and that greater improvements need to be made regarding study design and procedures. Although blinding of participants has ethical implications, blinding of clinicians recording the outcome measures was not practised commonly. In scoring systems that require completion by an investi-

gator, it is recommended that the investigation be carried out by an independent investigator to ensure accurate responses from the patient avoiding risk of bias through patient-investigator relationships. Several authors contributed to multiple studies included in this review introducing a risk of bias in both study design and reporting of outcomes across the studies.

The studies included in this review were not directly comparable due to differences in study design, lesions, surgical technique, follow-up and outcome measures. Although the AOFAS score was used in all three ankle studies and the mHHS in two of the three hip studies, there were no consistent scoring systems used for the knee studies. Nevertheless, a pattern of positive patient outcomes can be seen across all of the studies. Future studies should incorporate a universal method of rating patient outcomes for each joint location, allowing direct comparison of results. There also is a need to determine whether MRI assessment is a reliable tool as the studies in our review suggest that it does not necessarily correspond with patient outcome measures. Nevertheless, we recommend that all studies should continue to carry out an MRI assessment while further evidence on its relevance is sought.

Many of the studies included patients that required additional surgical procedures including osteotomies. For a patient undergoing more than one surgical procedure it would be difficult to determine the effect of each procedure in relieving pain and improving joint function. There is a distinct lack of consensus regarding post-operative management and the structure of rehabilitation programmes. Rehabilitation programs can have a significant influence on patient outcomes and recovery rates. Although it is difficult to develop a universal rehabilitation program due to the large number of variables such as patient demographics, and

lesion size and location, this needs to be considered when comparing outcomes between different studies. Due to the variation in studies it is not possible to determine if the type of scaffold, surgical technique or rehabilitation regime affect the outcome.

Limited studies suggest that femoral condyle lesions do better than patellar lesions, and osteochondral defects do better than chondral lesions. Defect sizes did not generally have an effect on the patient's outcome unless the defect was > 8 cm², in which case it had a detrimental effect on outcomes. There is limited evidence that younger patients experience greater improvements than older patients and display better recovery rates. It has been shown *in vitro* that bone marrow stem cells from older patients have reduced chondrogenic potential compared with younger patients, potentially decreasing the effectiveness of AMIC in older patient groups.

Follow-up period is an important factor in assessing the real effectiveness and reliability of the AMIC procedure. Since the treatment method is relatively new, there is a lack of long-term patient outcome data available. A longer follow-up period allows the proper assessment of long term outcomes for a procedure. Although five-year follow-up was available for two studies^[30,31], the patients had all undergone additional procedures making any improvements difficult to attribute to the AMIC procedure alone. It was demonstrated in the study conducted by Gille *et al.*^[26] and Gudas, Gudas *et al.*^[27] that declines in clinical outcomes can be observed as early as 18 to 24 mo after undergoing surgical treatment without additional procedures. Patient assessed outcomes by Gille *et al.*^[26] declined significantly between the 24 mo and 48 mo post-operative period, indicating that there may be concerns regarding durability of the repaired cartilage after undergoing the AMIC procedure. In the randomized control trial by Anders *et al.*^[3] improvements in pain scores and patient outcomes, including Cincinnati scores, were observed at 12 mo follow-up. Between 12 and 24 mo follow-up, although 12 patients showed further improvement in Cincinnati scores, 12 showed little or no change, and 3 showed a decline. This supports the observation by other studies, and their 5-year follow-up results are awaited.

The published literature reviewed suggests that AMIC in cartilage repair is a safe and effective treatment option that improves patient outcome measures and reduces pain. MRI findings however do not necessarily correspond with patient outcome measures. Most studies reported promising results, with no mention of further surgical corrections being needed in the follow-up period. Medium- and long-term results for AMIC procedures without additional surgeries are awaited. Earlier studies suggest that AMIC results may peak at around 24 mo.

The CMS results suggest that the clinical trials evaluated in this systematic review were of fair to reasonable quality; with 8 of the 15 studies achieving

total CMS scores ranging from 60 to 80. The main weaknesses across the studies were the total number of participants and the patient follow-up periods. Improvements in these areas will significantly increase the reliability of the patient outcome measures, while allowing investigators to draw more definitive conclusions. More high level studies with larger sample sizes, and extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

COMMENTS

Background

The results with autologous matrix-induced chondrogenesis (AMIC) in the literature have been variable. As there are limited studies on AMIC, variability in the type of scaffold used, the surgical procedure, defect size and location, and patient variability may all contribute to variable results. In addition, we are not aware of the longevity of these results.

Research frontiers

AMIC is a one-step procedure that brings together microfracture with a collagen matrix scaffold. There is increasing interest in AMIC as it provides a cost-effective alternative to cell-based therapies for articular cartilage repair, and it is highly autologous in nature.

Innovations and breakthroughs

The published literature reviewed suggests that AMIC in cartilage repair is a safe and effective treatment option that improves patient outcome measures and reduces pain. MRI findings however do not necessarily correspond with patient outcome measures. Most studies reported promising results, with no mention of further surgical corrections being needed in the follow-up period. Medium- and long-term results for AMIC procedures without additional surgeries are awaited.

Applications

More high level studies with larger sample sizes, and extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Terminology

Mesenchymal stem cells (MSCs): These cells reside in bone marrow and many adult tissues. MSCs are multipotent stromal cells capable of self-renewal and differentiation *in vitro* into a variety of cell lineages, including chondrocytes, osteoblasts, and adipocytes. They are therefore seen as an optimal regenerative cellular therapeutic for musculoskeletal regeneration.

Peer-review

This is a well-designed and written systematic review.

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P- Reviewer: Gheita TA, Zhou S **S- Editor:** Ji FF **L- Editor:** A
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