

# One-stage vs two-stage cartilage repair: a current review

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**Introduction:** Articular cartilage has a poor capacity for regeneration if damaged. Various methods have been used to restore the articular surface, improve pain, function, and slow progression to osteoarthritis.

**Method:** A PubMed review was performed on 18 March, 2010. Search terms included “autologous chondrocyte implantation (ACI)” and “microfracture” or “mosaicplasty”. The aim of this review was to determine if 1-stage or 2-stage procedures for cartilage repair produced different functional outcomes.

**Results:** The main procedures currently used are ACI and microfracture. Both first-generation ACI and microfracture result in clinical and functional improvement with no significant differences. A significant increase in functional outcome has been observed in second-generation procedures such as Hyalograft C, matrix-induced ACI, and ChondroSelect compared with microfracture. ACI results in a higher percentage of patients with clinical improvement than mosaicplasty; however, these results may take longer to achieve.

**Conclusion:** Clinical and functional improvements have been demonstrated with ACI, microfracture, mosaicplasty, and synthetic cartilage constructs. Heterogeneous products and lack of good-quality randomized-control trials make product comparison difficult. Future developments involve scaffolds, gene therapy, growth factors, and stem cells to create a single-stage procedure that results in hyaline articular cartilage.

**Keywords:** autologous chondrocyte implantation, microfracture, cartilage repair

## Introduction

The field of cartilage repair continues to challenge William Hunter’s famous statement made in 1743: “If we consult the standard surgical writers from Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to be a very troublesome disease; and that when destroyed, it is not recovered”.<sup>1</sup> With the conception of cell-based techniques and the publication by Brittberg et al<sup>2</sup> it has been shown that hyaline-like cartilage can be regenerated using autologous chondrocyte implantation (ACI). Alternatively, subchondral bone violation or marrow stimulation techniques have been used to create a fibrocartilage repair. These techniques of cartilage regeneration have the potential to be applied to a large population; with a review of 31,516 arthroscopies demonstrating that 63% had a chondral lesion.<sup>3</sup> Of these lesions, 20% were considered to be grade 4 (osteochondral defects) on the Outerbridge scale. These lesions can arise from acute trauma, overuse, ligamentous instability, malalignment, meniscectomy, or osteochondritis dissecans.<sup>4</sup> This initial chondral insult results in a proinflammatory milieu, with tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$

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**Figure 1** Cadaveric knee demonstrating MACI graft on medial femoral condyle.

(IL-1 $\beta$ ) playing a key role in osteoarthritis pathogenesis.<sup>5</sup> These cytokines directly inhibit cartilage extracellular matrix (ECM) production and induce inflammatory and degradative cytokines, chemokines, matrix metalloproteinases, and aggrecanases.<sup>5</sup> Thus, the initial chondral injury can result in a process that can degrade the entire articular surface over time.

Single-stage procedures that have been used to treat articular cartilage defects include microfracture, abrasion arthroplasty, subchondral drilling, osteochondral autograft/allograft transfer, and perichondrial/periosteal transplantation. Two-stage procedures are typified by the ACI procedure, where an initial arthroscopy is used to harvest chondrocytes for culture. The second stage involves the implantation of the cultured chondrocytes into the defect, either openly or arthroscopically. Novel developments include the use of allografts, mesenchymal stem cells, gene therapy, growth factors, and scaffolds to attempt to develop a single-stage procedure capable of producing hyaline cartilage. In all procedures, we advocate correcting anatomical abnormalities such as tibiofemoral or patellofemoral malalignment, ligamentous insufficiency, meniscal deficiency, and subchondral bone loss to create a mechanical environment commensurate to cartilage repair.

## Methodology

A PubMed review was performed on 18 March, 2010. Search terms included “ACI” and “microfracture” or “mosaicplasty”. Sixty-eight studies were identified, and abstracts were analyzed. Four randomized trials and 1 nonrandomized trial compared ACI with microfracture. Three randomized trials compared ACI with mosaicplasty. A lack of proper control

group was present in all trials. A title search of 903 trials in relation to ACI, microfracture, and mosaicplasty was also performed.

## Single-stage cartilage repair Arthroscopic washout/debridement/ abrasion arthroplasty

Arthroscopic washout and debridement are considered to be palliative procedures as they do not restore the articular surface. Variable rates of improvement in symptoms have been reported between 40% and 68% at 2-years follow-up.<sup>6,7</sup> However, a good-quality randomized controlled trial by Moseley et al<sup>8</sup> have not shown any difference between arthroscopic washout, debridement, or placebo surgery. Abrasion arthroplasty is an extensive multitissue debridement, used as a palliative procedure in patients seeking to avoid total knee replacement. This procedure stimulates a fibrocartilage repair that has been shown to persist for many years, but it does not possess the biomechanical properties of hyaline cartilage.<sup>9</sup>

## Microfracture

In the microfracture technique, the subchondral bone is violated with an awl, allowing bleeding and the passage of mesenchymal stem cells, red blood cells, platelets, fat, and growth factors from the bone marrow.<sup>10</sup> Mesenchymal stem cells are multipotent stem cells that can differentiate into a variety of lineages, including chondrocytes, osteoblasts, adipocytes, and myocytes. This allows a predominantly fibrocartilage repair with a varying amount of hyaline cartilage. Over an average 11-year follow-up, Steadman et al<sup>10</sup> have demonstrated improvements in Lysholm and Tegner scores, with 80% of patients at 7 years considered improved. Solheim et al<sup>11</sup> performed 5-year follow-up on 110 patients. Twenty-two percent of cases were considered to be failures, by virtue of requiring reoperation. Of the successful cases, there was a significant improvement in Lysholm scores, mean pain scores, and mean functional scores, with improvement being the greatest in patients who had single chondral lesions. A systematic review by Mithoefer et al<sup>12</sup> of 28 studies and 3,122 patients treated with microfracture showed an improvement in knee function in all studies to 24 months, with variable results after this time frame. A variation of this technique, subchondral drilling has been used to stimulate fibrocartilaginous repair, with improvement in functional outcome.<sup>13</sup> Microfracture has become the dominant technique by virtue of being able to be performed arthroscopically.

**Table I** Comparison of single-stage procedures for cartilage repair

Procedure	Treatment acceptance criteria	Durability and efficacy
Arthroscopic washout and debridement	Mechanically significant loose body or meniscal tear.	No more effective than placebo surgery in the treatment of osteoarthritis.
Microfracture	Outerbridge grade 3 or 4 contained chondral defects. Lesion size <4 cm <sup>2</sup> .	Revision rate of 23%–32% at years 2–5 in randomized studies. Improved functional scores in all studies at 24 months; however, results from long-term durability are conflicting.
Autologous osteochondral implantation	Full thickness osteochondral defects 1–4 cm <sup>2</sup> .	Good to excellent functional scores between 79% and 92% observed at 10-year follow-up. 3% of patients had long-term morbidity from donor site.
Allograft osteochondral transplantation	Full thickness osteochondral lesions >3 cm <sup>2</sup> and 1 cm deep.	Clinical improvement has been shown up to 2 years in small nonrandomized studies.
Synthetic cartilage – Salucartilage™	Outerbridge grade 4 chondral lesions.	Functional improvement demonstrated at 1-year follow-up. 4% rate of implant failure at 1 year.
Scaffold – TruFit™ plug	Used to backfill donor sites in autologous osteochondral grafting. Being investigated as primary treatment for articular defects.	Safety and effectiveness in primary treatment of osteochondral defects has not been demonstrated.
Scaffold – VeriCart™	Used in conjunction with microfracture or rehydrated with bone marrow.	Currently undergoing trials.
Scaffold – BST CarGel®	Hydrogel scaffold used in conjunction with microfracture.	Currently undergoing trials.
Scaffold – GelrinC	Hydrogel scaffold used in conjunction with microfracture.	Currently undergoing trials.
Scaffold – DeNovo® ET	Scaffold-free living cartilage implant consisting of allogeneic fetal chondrocytes.	Shown to integrate with surrounding cartilage in sheep model.

### Enhanced microfracture techniques

Enhanced microfracture involves combining the traditional procedure with a scaffold. This is a growing area of interest due to the benefits of a single-stage procedure. Theoretically, the addition of a scaffold may give the mesenchymal stem cells additional support and may distribute them more evenly throughout the defect compared with microfracture alone. Steinwachs et al<sup>14</sup> have described the surgical technique for combining microfracture with a type I/III collagen bilayer membrane (Chondro-Gide®; Geistlich, Wolhusen, Switzerland). The membrane is secured into the defect with fibrin glue. Preliminary results have been published at the EFORT congress in 2007, with patients showing clinical and radiological (magnetic resonance imaging [MRI]) improvement.<sup>15</sup> Erggelet et al<sup>16</sup> have trialed a polyglycolic acid/hyaluronan-based scaffold (Chondrotissue®; Biotissue AG, Zurich, Switzerland) compared with microfracture alone in an ovine model. Significantly more type II collagen and a more cartilaginous-like appearance were demonstrated compared with the microfracture controls. Other scaffolds that are in development for use with microfracture are ASEED® (Interface Biotech, Hoersholm, Denmark), a copolymer consisting of methoxy polyethylene glycol/poly lactic-co-glycolic acid; VeriCart™ (Histogenics, Waltham, MA, USA),

a collagen-based scaffold; BST – CarGel® (Biosyntech, Laval, Quebec, Canada), a chitosan-glycerol phosphate scaffold; and GelrinC (Regentis, Or-Akiva, Israel), a photopolymerizable PEGylate fibrinogen liquid.<sup>17,18</sup> Hydrogels have a high water content that creates a protective environment which mimics native cartilage.<sup>19</sup> They allow the addition of growth factors and cell signaling molecules that can diffuse freely.<sup>20</sup> The addition of bone morphogenetic peptide-7 (BMP-7) has been shown to improve the repair histology when used in addition to microfracture.<sup>21</sup>

### Autologous osteochondral transfer

Autologous osteochondral transfer involves harvesting an osteochondral plug from a minimal weight-bearing area of the knee, such as the peripheries of the patellofemoral joint, and transferring it to the chondral defect.<sup>22</sup> Commercially available systems include the mosaicplasty system (Smith and Nephew, Andover, MA, USA) and the osteochondral autograft transfer system (OATS®; Arthrex, Naples, FL, USA). The ideal diameter of the defect is between 1 and 4 cm<sup>2</sup>. This method has been used for defects in the tibiofemoral joint, patellofemoral joint, talar, humeral capitellar, and femoral head.<sup>23</sup> Excellent functional outcome was reported in 79%–92% of patients depending on the location of the chondral defect in the knee.

**Table 2** Comparison of 2-stage procedures for cartilage repair

Procedure	Treatment acceptance criteria	Durability and efficacy
ACI	Full thickness symptomatic chondral lesion >2 cm <sup>2</sup> .	Multiple case series demonstrating clinical and functional improvement at 2–10 years. A failure rate of 16% has been reported at this time.
MACI®	Full thickness symptomatic chondral lesions >2 cm <sup>2</sup>	Multiple case series demonstrating clinical improvement. Greater number of patients with good to excellent clinical scores compared with collagen-covered ACI (not statistically significant). Graft failure rate between 0%–6.3%.
Hyalograft® C	Full thickness symptomatic chondral lesions >2 cm <sup>2</sup>	Multiple studies demonstrating clinical improvement at 2–5-year follow-up. Failure rates as low as 7% in normal knees, increasing to 82% with concomitant pathology.
Characterized chondrocyte implantation (ChondroCelect®)	Symptomatic ICRS grade 3/4 defects of the femoral condyles. <sup>44</sup>	Significantly higher overall KOOS scores in CCI group compared with microfracture. Graft complications were reported in 5%.
Neocart®	Full thickness lesion of the femoral condyle. <sup>43</sup>	Initial 2 grafts failed. Remaining 8 grafts demonstrated improved function.
CARTIPATCH®	Symptomatic ICRS grade 3/4 defects of the femoral condyles, lesion size 1–5 cm <sup>2</sup> .	Significantly improved IKDC subjective scores at 2-years follow-up. Significantly decreased lesion size on repeat MRI scans at 2-years follow-up (2.7–0.4 cm <sup>2</sup> ).

**Abbreviations:** ACI, autologous chondrocyte implantation; MACI, matrix-induced autologous chondrocyte implantation; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging.

Three percent of patients experienced problems with long-term donor site morbidity. Of 83 patients, 69 patients who underwent repeat arthroscopy demonstrated good gliding surfaces, with histological evidence of survival of hyaline cartilage and fibrocartilage repair at the donor site. Jakob et al<sup>24</sup> have shown that 86% of their patients demonstrated better functional outcome at 2-years follow-up. Issues with the procedure include technical difficulty and donor site morbidity.<sup>22,23</sup> It is assumed that a fibrocartilage repair will form at the donor site; however, both hypertrophy and lack of regrowth have been reported, with an associated increase in joint stiffness.<sup>25,26</sup> Chondrocyte death at the margins of the plug may lead to graft failure and impede lateral graft integration.<sup>13</sup> These parameters can be assessed on postoperative MRI including the donor and recipient sites.<sup>27</sup>

### Allograft osteochondral transplantation

Allograft osteochondral transplantation offers the benefits of a single-stage procedure; however, due to advancements in other techniques, the use is limited to lesions with an area >3 cm<sup>2</sup> and 1 cm deep.<sup>28,29</sup> Limited studies have been published in the literature. Garret<sup>30</sup> demonstrated clinical improvement in all patients who underwent fresh allograft transfer to the femoral condyle. A total of 11 patients had a second arthroscopy, with all grafts considered viable, and 2 patients demonstrated fraying at the edge. Czitrom et al<sup>31</sup> demonstrated chondrocyte viability in 4 patients posttransplantation. Allografts are viable for 28 days in

media storage; however, a shorter duration is favorable due to adverse effects associated with long storage.<sup>11</sup> Although articular cartilage is considered to be an immuno-privileged area, problems with immuno-rejection and a theoretical risk of infection have been described.<sup>32,33</sup>

### Periosteal/perichondrial grafting

Periosteal grafting involves securing autologous periosteum into the cartilage defect. The mesenchymal stem cells in the cambium layer have an ability to form hyaline-like cartilage. Periosteum is more often used than perichondrium due to accessibility. Lorentzon et al<sup>34</sup> demonstrated good to excellent functional outcome in all patients who underwent grafting to patella defects. Biopsy from 5 random patients showed hyaline-like cartilage. Unfortunately, periosteal or perichondrial transplantation cannot be advocated as an exclusive procedure due to the high rate of endochondral ossification and graft failure.<sup>17,35</sup>

### Synthetic cartilage constructs

Synthetic constructs offer an alternative single-stage procedure to biological resurfacing. The prosthesis must be able to withstand weight-bearing forces and create a low friction environment for the opposing cartilage surface.<sup>18</sup> Friction-wear debris and micromotion are the main contributors to osteolysis and periprosthetic inflammation.<sup>18</sup> SaluCartilage™ (Salumedica, Atlanta, GA, USA) is a polyvinyl alcohol hydrogel. Lange et al<sup>36</sup> performed 49 procedures

**Table 3** Summary of randomized trials comparing 1-stage vs 2-stage procedures

Procedure and author	Study size and follow up	Outcome
First-generation ACI vs microfracture	40 patients were randomized to both ACI and microfracture. Patients were assessed at 5-year follow-up.	Significant improvements in Lysholm, visual analog pain scores, and SF-36 scores with no differences between groups. No significant difference in the rate hyaline and fibrocartilage was found on repeat biopsy.
First-generation ACI vs microfracture	77 patients randomized between ACI and microfracture. Patients assessed at 2-year follow-up.	70% of patients returned to >85% symmetry in functional performance. No significant difference between groups.
ChondroCelect vs microfracture	57 patients randomized to ChondroCelect and 61 to microfracture. Patients assessed at 3-year follow-up.	Mean improvement in KOOS was greater in the ChondroCelect group than microfracture. MRI assessment showed subchondral bone worsened in the microfracture group compared with ChondroCelect. Failure rates of 3.9% in ChondroCelect group compared with 11.5% in microfracture.
MACI vs microfracture	40 patients randomized to MACI and 20 to microfracture. Patients assessed at 2-year follow-up.	Significantly better results in the MACI group using Lysholm, Tegner, ICRS patient, and ICRS surgeon scores.
Hyalograft C vs microfracture	Nonrandomized study with 40 patients allocated to Hyalograft C and 40 to microfracture. 5-year follow-up.	Significantly better outcome in Hyalograft C group at 5-year follow-up as assessed by IKDC and Tegner scores.
First-generation ACI vs mosaicplasty	58 patients randomized to ACI and 42 to mosaicplasty. Mean follow up of 19 months.	88% of ACI patients achieved a good to excellent result using the Cincinnati and modified Stanmore scoring systems compared with 69% of mosaicplasties. Arthroscopic evaluation at 1 year demonstrated good to excellent ICRS scores in 82% of ACI compared with 34% of mosaicplasty.
First-generation ACI vs mosaicplasty	20 patients randomized to ACI and 20 to mosaicplasty. 2-year follow-up.	Significantly lower Lysholm scores at 6-, 12-, and 24-month follow-up in the ACI group.
First-generation ACI vs mosaicplasty	47 patients randomized to ACI or mosaicplasty. 23 patients were followed up over 3 years.	Lysholm score was improved in both groups at 3 years, with no significant difference between groups.

**Abbreviations:** IKDC, International Knee Documentation Committee; ACI, autologous chondrocyte implantation; KOOS, knee injury and osteoarthritis outcome score; MRI, magnetic resonance imaging; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee.

for Outerbridge grade 4 chondral lesions. One-year follow-up demonstrated an improvement in functional outcome; however, 2 implants failed, and MRI scanning revealed edema at the implant/bone interface. ABS Chondrocushion® (ABS Corporation, Minnetonka, MN, USA) is a plug implant made from biocompatible polyurethane. It is a copolymer structure, with a hard base for bone implantation and a soft surface as the cartilage interface.<sup>18</sup> As yet, no data have been published. Carticept Medical Inc (Alpharetta, GA, USA) is currently developing a polyvinyl alcohol hydrogel. Animal studies are currently underway.<sup>18</sup>

Scaffolds are similar to synthetic constructs, but it has been engineered to permit in-growth and resorption to foster cartilage repair.<sup>18</sup> Scaffolds have been used in ACI to secure chondrocytes to the cartilage defect. Additionally, they provide an environment conducive for differentiated chondrocytes to produce ECM. The TruFit™ plug

(Osteobiologics/Smith and Nephew, Memphis, TN, USA) is a polyglycolate-calcium sulfate polymer that has been used to fill the donor site in the OATS procedure. It is being investigated in the filling of weight-bearing defects on the femoral condyles.<sup>18</sup> VeriCart is a porous collagen-based scaffold designed to attract chondrocytes to form cartilage.<sup>37</sup> It is currently undergoing trials where the matrix is rehydrated with bone marrow.

## Two-stage cartilage repair ACI

The ideal patient for ACI is a symptomatic, full thickness chondral or osteochondral lesion, surrounded by healthy normal cartilage.<sup>38</sup> However, uncontained lesions can be treated with a variety of anchors and sutures. Malalignment, ligamentous insufficiency, and meniscal deficiency can be corrected at the time of harvest. ACI may be considered



as primary treatment for lesions  $>2$  cm<sup>2</sup>. Contraindications include bipolar lesions, osteoarthritic degeneration, rheumatoid arthritis, active autoimmune connective tissue disease, and concomitant malignancy.<sup>38</sup> Although arthroscopic assessment of chondral defects remains the optimal means of evaluation, MRI is increasingly becoming a noninvasive method of diagnosing chondral and osteochondral injuries of the knee, with reported sensitivity up to 99%.<sup>39–41</sup> This reduces the need for arthroscopy before the first-stage procedure. The first stage of the procedure requires arthroscopic harvest of chondrocytes from a nonweight-bearing region of articular cartilage.<sup>2,40,42</sup> After culture of 4–6 weeks, a second-stage procedure is used to implant chondrocytes into the defect. The second stage involves debridement of the cartilage edges, then chondrocyte implantation into the defect, secured under a sutured periosteal membrane that is sealed with fibrin glue to create a watertight construct.<sup>38,40,42</sup> We favor the use of the second-generation, matrix-induced ACI (MACI®; Genzyme, Boston, MA, USA) procedure, in which chondrocytes are seeded onto a type I/III collagen bilayer. This had decreased donor site morbidity as no periosteum is needed, is technically less demanding as no suturing is required, and has lower risk of graft hypertrophy. An alternative product is Hyalograft® C (Fidia Advanced Biopolymers, Italy), a hyaluronan-based scaffold.<sup>20</sup> NeoCart® (Histogenics, Waltham, MA, USA) is a second-generation technique where autologous chondrocytes are cultured on a 3-dimensional type I bovine collagen matrix.<sup>43</sup> This matrix/chondrocyte construct is then cultured in a “bioreactor” under hydrostatic pressure with the aim of preventing chondrocyte dedifferentiation.<sup>43</sup> ChondroCelect® (TiGenix NV, Leuven, Belgium) is an autologous cell therapy that introduces the concept of chondrogenic potential, whereby a gene marker profile is used to determine *in vivo* cartilage-forming potential.<sup>44</sup> CARTIPATCH® (Tissue Bank of France, Lyon, France) is an ACI product that uses an agarose–alginate hydrogel scaffold that is preformed into 10-, 14-, and 18-mm plugs. The plug is secured into the defect by drilling 4-mm deep holes in the subchondral bone that conform to the plug shape. Good functional improvement has been described for ACI, MACI, Hyalograft C, ChondroCelect, and CARTIPATCH.<sup>4,44–51</sup>

## Arthroscopic ACI

Both MACI and Hyalograft C have been implanted arthroscopically. Potential benefits include smaller incisions and a decreased incidence of adhesions and arthrofibrosis.

Ergellet et al<sup>52</sup> have described arthroscopic implantation of the MACI implant, with transosseous fixation to the defect. A case of implantation using fibrin glue for fixation has also been described.<sup>53</sup> Marcacci et al<sup>54</sup> have described the arthroscopic technique for implantation of the Hyalograft C implant. The implant is secured into the defect by its intrinsic adhesive properties, without the need for glue or suturing. Arthroscopic Hyalograft C implantation has been described for tibiofemoral, patellofemoral, and talar dome lesions.<sup>47,55,56</sup>

## Rehabilitation postchondral repair

Postoperative rehabilitation after ACI emphasizes range of motion exercises and progressive load bearing.<sup>57</sup> Unloading and immobilization have been shown to cause proteoglycan loss and weakening.<sup>58</sup> Dynamic compression is the key to graft maturation, resulting in increased matrix synthesis. Static loads have been shown to decrease matrix synthesis.<sup>59</sup> An *in vitro* model on the chick limb bud has demonstrated that twice as many mesenchymal stem cells were committed to the chondrocytic phenotype when subjected to cyclical compression compared with static compression.<sup>60</sup> It is a balance between stimulating the chondrocytes through exercises without causing graft delamination and failure. Range of movement exercises are generally commenced 24 hours postsurgery to allow time for the graft to adhere. Full weight bearing is generally achieved between weeks 6 and 12, with the exception of the publication by Bentley et al<sup>22</sup> which commenced protected full weight bearing with the use of crutches at 24 hours postoperation.<sup>56,61,62</sup> A return to low-impact sports is delayed 6–12 months as guided by the clinical and radiological examinations. Return to high-impact sports is delayed 12–18 months. Microfracture offers a similar rehabilitation with 8 weeks of partial weight bearing postoperatively. Return to jumping and twisting sports can be considered at 4–6 months, as guided by the clinical examination.<sup>10</sup> Of note, the randomized control trials comparing ACI with microfracture or mosaicplasty have subjected both groups to the same postoperative rehabilitation. There is currently no data to suggest that rehabilitation is shorter or less intense with a 1-stage or 2-stage procedure. Results from our institution have been published by Ebert et al<sup>63</sup> comparing accelerated weight bearing (full weight bearing at 8 weeks) with delayed full weight bearing at 11 weeks. A total of 62 patients were randomized. No graft failures were observed in either group on MRI assessment at 3-months follow-up. Lower pain scores as measured by the knee injury and osteoarthritis outcome score (KOOS)

and greater improvement in the 6-minute walk test were observed in the accelerated weight-bearing group.

## Comparison of 1-stage vs 2-stage trials

### ACI vs microfracture

Knutsen et al<sup>64</sup> randomized 40 patients to be treated with ACI and 40 patients to be treated with microfracture. At 5-years follow-up, there were 9 failures in each group, as defined by requiring reoperation. Significant improvements were maintained in Lysholm scores, visual analog pain scale scores, and SF-36 scores with no significant differences between groups. A total of 67 patients underwent biopsy and histological evaluation. There was no significant difference in the frequency that hyaline cartilage and fibrocartilage were found in the 2 groups. About 24% of patients in whom the procedure did not fail demonstrated signs of osteoarthritis on radiograph at 5 years. There was no difference between groups. The conclusion was that both were acceptable forms of treatment, with 77% of patients having a good outcome at 5 years. Van Assche et al<sup>65</sup> have performed a similar sized study, randomizing 77 patients to ACI or microfracture. Mean defect size was 2.4 cm<sup>2</sup>. At 2 years, 70% of patients returned to >85% symmetry in functional performance, with both groups being similar.

A randomized control trial comparing characterized chondrocyte implantation (CCI, marketed as ChondroCelect) and microfracture has been published by Saris et al.<sup>44</sup> A total of 57 patients were randomized to CCI and 61 patients were randomized to microfracture. Follow up was over 36 months. The primary measure of clinical outcome was evaluated using the KOOS questionnaire. Mean improvement in KOOS over 36 months was significantly greater in the CCI group than in the microfracture group. MRI assessment showed that subchondral bone reaction worsened over time in the microfracture group compared with CCI group. Failure rates after 36 months were 3.9% in the CCI group compared with 11.5% in the microfracture group. CCI patients with a high gene profile score showed a greater improvement in mean overall KOOS score at 36 months compared with low gene profile scores.

Basad et al<sup>66</sup> have recently published a randomized study comparing MACI with microfracture for defects involving the femoral condyles or patella. Patient age was between 18 and 50 years. Single chondral lesions were selected, and defect size was between 4 and 10 cm<sup>2</sup>. Exclusion criteria included the presence of inflammatory or osteoarthritis, knee instability, meniscectomy, malalignment, obesity, and

subchondral bone loss. At 2-years follow-up, the MACI group demonstrated significantly higher mean Lysholm scores (92 vs 69). The median Tegner score was significantly higher at 2 years, with a score of 4 in the MACI group compared with 3 in the microfracture group. The International Cartilage Repair Society (ICRS) patient scores were significantly higher in the MACI group.

Kon et al<sup>66</sup> performed a nonrandomized study comparing the functional outcomes of microfracture with Hyalograft C. There were 40 patients in each group, and the mean defect size was 2.5 cm<sup>2</sup> for microfracture and 2.2 cm<sup>2</sup> for the Hyalograft C group. Only 1 case failed from the microfracture group, requiring reoperation. When comparing the 2 groups, the International Knee Documentation Committee's (IKDC) subjective and objective scores were significantly higher in the Hyalograft C group at 5 years. The Tegner score was similar between the 2 groups at 2-year follow-up; however, it deteriorated in the microfracture group between years 2 and 5. Both methods showed satisfactory improvement in medium-term follow-up with better clinical results in the Hyalograft C group.

### ACI vs autologous osteochondral transfer

Bentley et al<sup>22</sup> performed a randomized control trial comparing ACI to mosaicplasty. A total of 58 patients were randomized to ACI and 42 were randomized to mosaicplasty. Mean defect size was 4.66 cm<sup>2</sup>. Functional assessment using the modified Cincinnati and Stanmore scores showed a significant difference, with 88% of patients having a good to excellent result with ACI compared with 69% of patients after mosaicplasty. Of note, all 5-patella mosaicplasties failed. Arthroscopic evaluation at 1 year revealed a good to excellent ICRS score in 82% of ACI group compared with 34% of mosaicplasty group.

Horas et al<sup>67</sup> randomized 20 patients to ACI and 20 patients to autologous osteochondral transfer. Mean defect size was 3.75 cm<sup>2</sup>. Improvement in the ACI group was significantly slower than the osteochondral transfer group, with the Lysholm score being lower at 6, 12, and 24 months. Eight biopsies were taken from 6 patients in the ACI group in the first 24 months. Staining revealed a predominantly fibrocartilage repair. Three patients who underwent osteochondral transplantation had biopsies – the plugs retained their original hyaline appearance; however, fissuring persisted between plugs and native cartilage. Dozin et al<sup>61</sup> performed a study of ACI vs osteochondral transfer. Both groups showed functional improvement in Lysholm and IKDC scores at 3 years, with no significant difference between groups.

## Adjuncts to 1-stage or 2-stage cartilage repair

### Gene therapy/use of growth factors

Single-stage repair procedures that access the subchondral mesenchymal stem cells usually lead to a fibroblastic repair. Gene therapy and growth factors can be used to encourage mesenchymal stem cells to differentiate into the chondrocytic phenotype and ultimately produce hyaline cartilage. Gene therapy also has a role in ACI procedures in trying to maintain the chondrocytic phenotype during culture. Cytokines such as IL-10 have a direct stimulatory effect on collagen type II and proteoglycan expression.<sup>5</sup> Other leading candidates as growth factors include Insulin-like growth factor 1 (IGF-1), Transforming growth factor beta (TGF- $\beta$ ), Bone morphogenetic protein 2 (BMP-2), Bone morphogenetic protein 7 (BMP-7), and bFGF.<sup>68,69</sup> All of these enhance cartilage repair in animal models.<sup>70</sup> Due to the short half-life of these cytokines, genetic information must be introduced into the cell to allow endogenous production. The genetic information can be transferred by a vector, which may be classified as viral or nonviral. Viral vectors are altered “wild-type” viruses that rely on infection of the desired cell to deliver the genetic information.<sup>71</sup> Nonviral vectors include “naked” DNA, DNA in liposomes, and DNA matrix composite.<sup>71</sup> Viral vectors are an effective method of transferring genetic information; however, concerns remain about their oncogenic potential.<sup>71</sup> Grande et al<sup>72</sup> have demonstrated this in a rabbit model. The genes for sonic hedgehog and BMP-7 were inserted into periosteal mesenchymal stem cells and used for the repair of full thickness cartilage defects. The overexpression of these genes resulted in a smoother and more hyaline-like appearance compared with the controls.

## Mesenchymal stem cells and allogeneic fetal sources

The use of autologous chondrocytes for repair raises issues, such as donor site morbidity, low cell number upon harvest, and loss of chondrocytic markers in culture.<sup>73</sup> Mesenchymal stem cells are pluripotent cells that have the capacity to form bone, cartilage, tendon, and adipose tissue.<sup>69</sup> Bone marrow-derived mesenchymal stem cells are believed to be uniformly positive for markers such as CD29, CD44, CD71, CD90, and CD106 and negative for markers of the hematopoietic lineage including CD14, CD4, and CD45.<sup>73</sup> Autologous mesenchymal stem cells from the bone marrow can be accessed by procedures that violate the subchondral bone. Alternatively, 2 mL of mesenchymal stem cells can

be aspirated from bone marrow and cultured over 3 weeks to give a theoretical yield of 12.5–37.5 billion cells.<sup>13</sup> The implantation of uncommitted cells often leads to fibrocartilage formation indicating that the *in vivo* environment is not sufficient to induce chondrogenesis.<sup>73</sup> A switch from proliferation to differentiation of mesenchymal stem cells during culture is an inherent tendency that is influenced by cell density.<sup>74</sup> Dexamethasone and TGF- $\beta$  are considered essential for differentiation of human mesenchymal stem cells to chondrocytes. Wakitani et al have demonstrated cartilage repair in a rabbit model using autologous osteochondral mesenchymal stem cells.<sup>91</sup> Additionally, fetal calf serum has been shown to increase osteochondral mesenchymal stem cell to chondrocyte differentiation during *in vitro* culture.<sup>75</sup> Allogeneic chondrocytes from fetal sources are being trialed in the DeNovo<sup>®</sup> ET (ISTO, St Louis, MO, USA) product, a biocompatible chondro-conductive/inductive matrix.<sup>76</sup> Theoretical advantages of fetal chondrocytes are their ability to produce more ECM and their nonimmunogenic nature.<sup>69,76</sup> The DeNovo ET implant is a single stage, off-the-shelf procedure that can be implanted arthroscopically or by mini-open approach. DeNovo ET has been shown to be able to integrate with surrounding cartilage and subchondral bone, while retaining its hyaline properties in a sheep model.<sup>9</sup>

## Discussion

The studies comparing first-generation ACI to microfracture showed improvement in both groups with no significant differences. However, Hyalograft C, MACI, and Chondro-Select have demonstrated better functional outcomes than microfracture. Although microfracture is a simple procedure, it should be used judiciously in large lesions after Minas et al<sup>77</sup> demonstrated that ACI has a 3 times higher failure rate when used as a salvage procedure after failed microfracture. This is due to a propensity of bony overgrowth following microfracture. Brown et al<sup>78</sup> demonstrated MRI evidence of bony overgrowth in 42 of 86 microfracture procedures. Blanke et al<sup>79</sup> have demonstrated significant bony overgrowth following microfracture in a porcine model. An exposed subchondral bone plate following microfracture was associated with significantly more overgrowth than if the defect was covered with an ACI graft.

Difficulties in comparing studies must be considered including low methodology scores, lack of control groups, and heterogeneous products (eg, first-generation and second-generation ACI).<sup>80</sup> Significant ambiguity exists within the literature regarding the classification of cell-based repairs. For simplicity, we have classified the original periosteal-covered



graft as first generation and all subsequent matrix-like repairs (MACI, Hyalograft C, NeoCart, and CARTIPATCH) as second generation. Third-generation products are 1-stage procedures using stem cells, growth factors, and matrix that produce a hyaline-like repair. This classification is arbitrary, and future products must be assessed by a method of cell culture and graft type. Although both generations offer improvements in functional outcome, second-generation autologous chondrocyte techniques are demonstrating a superior functional outcome. This may be due to slowing chondrocyte dedifferentiation in culture, resulting in a higher number of viable chondrocytes at implantation and a more hyaline-like repair. Use of a scaffold may result in a more even distribution of chondrocytes within the chondral defect.

Good functional results have been demonstrated with osteochondral transfer; however, ACI is becoming the preferred procedure because of its simplicity and lower donor site morbidity. These 2 factors are enhanced further in the second-generation ACI techniques that use scaffolds instead of periosteum.

In our treatment algorithm, we consider the use of MRI essential in the initial evaluation of osteochondral lesion size and location. This obviates the need for an arthroscopy before first-stage arthroscopy and biopsy in ACI or arthroscopy and treatment in microfracture. Regardless of the type of cartilage repair being performed, malalignment, ligamentous/meniscal deficiency, and subchondral bone loss should be corrected to create an environment conducive to cartilage repair. This is commonly performed at the time of treatment. A single-stage procedure such as microfracture is recommended for the treatment of lesions  $<2\text{ cm}^2$ . This has the benefits of 1 procedure, minimally invasive arthroscopy, relative simplicity, and cost efficiency compared with mosaicplasty or ACI. A review of the microfracture technique has demonstrated better functional outcomes with knee lesion size  $<4\text{ cm}^2$ , with an even smaller threshold of  $2\text{ cm}^2$  for the demanding athlete.<sup>12</sup> Better outcomes are also seen in the younger age group, with a cut-off age between 30 and 40 years.<sup>12</sup> We would recommend treatment of a  $2\text{--}4\text{ cm}^2$  lesion with a second-generation ACI repair due to better functional outcome.<sup>44,56,66</sup> Microfracture may be considered for the lower function individual. Lesion size  $>4\text{ cm}^2$  should be treated with a second-generation ACI procedure due to better functional outcome than microfracture. Second-generation ACI also benefits from operative simplicity compared with mosaicplasty or allograft transfer.

One-stage procedures appear to be attractive as they offer a single surgery. However, an arthroscopy will usually be required preoperatively to accurately assess the chondral

lesion. Additionally, most 1-stage procedures (with the exception of microfracture) are performed by an open approach. Second-generation ACI procedures such as MACI and Hyalograft C can be implanted arthroscopically. If a preoperative MRI is used to assess the chondral lesion, diagnostic arthroscopy can be combined with cartilage harvest.

Results from our institution have been published analyzing the histological outcome after MACI grafting.<sup>81</sup> Of a cohort of 56 patients, 11 patients consented to graft biopsy. Nine grafts were biopsied between 6 and 18 months. Seven of these grafts had a histological appearance consistent with hyaline cartilage and stained highly positive for type II collagen. One graft had a mixed hyaline/fibrocartilage appearance. The last graft demonstrated a fibrocartilage repair. Animal studies have also been performed at our institution to establish the efficacy of the MACI graft.<sup>82</sup> A randomized trial using a rabbit model has compared the MACI graft with untreated controls. Defects were created in the femoral condyle of rabbits and were analyzed for repair at 12 weeks. The untreated group uniformly demonstrated a disorganized fibrocartilage repair. The group treated with MACI showed a significantly more hyaline-like repair at 12 weeks.

## Suggested treatment algorithm flowchart

### Conclusion

Future developments to a single-stage procedure that restores native hyaline cartilage will involve mesenchymal stem cells combined with a matrix and appropriate growth factors (eg, TGF- $\beta$  and BMPs) to encourage mesenchymal stem cells to differentiate down the chondrocytic pathway. Many studies are currently in progress involving enhanced microfracture techniques, with some limited data demonstrating clinical improvement. However, the difficulty in accessing mesenchymal stem cells and not hematopoietic cells during marrow stimulation remains. Allogeneic mesenchymal stem cells from fetal sources may hold the most promise, as they can be isolated and cultured in a specific *in vitro* environment with appropriate growth factors, matrix, and hydrostatic pressure, resulting in differentiation down the chondrocytic pathway. This may allow for a mass produced off-the-shelf single-stage procedure. Phase I trials of DeNovo ET are underway, and the results are awaited.

Our current recommendation for the patient who has a symptomatic full thickness chondral lesion  $>4\text{ cm}^2$  would be a second-generation ACI repair, such as MACI or Hyalograft C for the reasons of simplicity, no morbidity of periosteal harvesting, and ability to generate a hyaline-like

repair.<sup>82</sup> Microfracture remains an acceptable technique for lesions <2 cm<sup>2</sup>. Lesions between 2 and 4 cm<sup>2</sup> can be treated with ACI or microfracture as first-line therapy, depending on the activity level of the patient, surgeon preference, and resource availability.

## Disclosure

The authors report no conflicts of interest in this work.

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