ORTHOPAEDIC SURGERY

ANZJSurg.com

Autologous chondrocyte implantation: an overview of technique and outcomes

Lachlan Batty,* Samuel Dance,† Sarvottam Bajaj‡ and Brian J. Cole§

*The Alfred Hospital, Prahran, Victoria
†Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia and
‡Midwest Orthopedics at Rush, Rush University Medical Center, Chicago, Illinois
§Departments of Orthopedics & Anatomy and Cell Biology, Division of Sports Medicine; and Cartilage Restoration Center at Rush, Midwest Orthopedics at Rush, Rush University Medical Center, Chicago, Illinois, USA

Key words
Autologous chondrocyte implantation, articular cartilage, chondral lesions, knee.

Abbreviations
ACI, Autologous Chondrocyte Implantation; MACI, matrix-induced autologous chondrocyte implantation.

Correspondence
Professor Brian J. Cole, 1611 W Harrison Street, Suite 300, Rush University Medical Center, Chicago, IL 60612, USA. Email: bcole@rushortho.com

L. Batty MBBS (Hons), BMedSc (Hons); **S. Dance** MBBS; **S. Bajaj** BE; **B. J. Cole** MD, MBA

Accepted for publication 4 March 2010.

doi: 10.1111/j.1445-2197.2010.05495.x

Abstract

Articular cartilage is susceptible to damage; however, it has limited capacity for repair. Damage can lead to persistent symptoms including pain, swelling, and loss of function and may ultimately progress to symptomatic degeneration of the joint. To restore function and minimize symptoms, many advocate surgical intervention in selected candidates, which can range from arthroscopic debridement to restorative procedures depending on patient and lesion characteristics. Autologous Chondrocyte Implantation (ACI) is a two-stage, typically second-line intervention where cultured autologous chondrocytes are used with the aim of resurfacing symptomatic chondral defects with hyaline or hyaline-like cartilage. Careful patient selection is important. We present an overview of this procedure including indications and contraindications, surgical technique, and post-operative management. A review of published ACI outcomes is then presented.

Introduction

Articular cartilage is susceptible to damage from acute high-energy forces and from repetitive shear and torsional forces applied to the superficial surface.[1] Despite this vulnerability, articular cartilage has limited capacity for regeneration and repair because of poor vascular supply and the deficiency of an undifferentiated cell population capable of migrating and responding to the insult.[2] Therefore, pain, swelling and mechanical symptoms caused by articular cartilage lesions can be ongoing, lead to loss of function, and ultimately, lead to symptomatic joint degeneration.

There are numerous surgical methods utilized for the management of articular cartilage defects with the aim of providing symptomatic relief and improving function. Arthroplasty is one option that has long been used in the treatment of degenerative joint disease with very satisfactory results. However, in younger, active patients with symptomatic focal chondral defects, arthroplasty is a less satisfactory treatment option. Such situations have prompted increasing acceptance of 'biologic' treatment solutions when used judiciously in carefully selected patients. Non-arthroplasty solutions can be classified as palliative procedures (arthroscopic debridement), reparative procedures (microfracture) and regenerative procedures (osteochondral grafting and Autologous Chondrocyte Implantation (ACI)).[2] These methods are often used in a stepwise, graduated treatment regimen to optimize joint function and reduce pain.

Currently, arthroscopic debridement and microfracture are commonly used as first-line treatment for symptomatic focal chondral defects that are relatively small with minimal associated bone loss. Microfracture techniques result in the defect filling with fibrin clot, leading to the formation of reparative fibrocartilage. This has been shown to provide relief to patients with smaller lesions or with limited activity. Fibrocartilage, however, has limited resistance to sheer forces and in larger defects or in high-demand patients may not adequately relieve symptoms and restore function. Regenerative

procedures including ACI and osteochondral grafting can be used as second-line measures in this situation to repair chondral or osteochondral defects with hyaline or hyaline-like cartilage. Hyaline cartilage is believed to have superior biomechanics and durability to fibrocartilage. This article provides an overview of ACI and reviews the literature assessing outcomes following ACI.

Indications and contraindications

Identifying appropriate candidates for ACI requires consideration of both patient and chondral defect characteristics. ACI is generally considered as a second-line treatment option after at least arthroscopic debridement or microfracture has produced an inadequate clinical outcome.[3] For example, one recent multi-centre report supported the role of ACI after failed treatment showing encouraging results with a 76% success rate.[4]

Patient age, body mass index (BMI), symptoms, occupation, level of sporting activity, willingness to engage in the rehabilitation and the patients' specific concerns are important to consider when contemplating ACI as a treatment option.[2] ACI is commonly performed on patients between 15 and 50 years of age. However, of greater importance than chronological age is physiological age and the underlying condition of the joint. Rehabilitation for ACI is extensive and demanding. Patients require motivation and living situations that are conducive for optimal results. More important is that achieving the ultimate clinical benefits following ACI may be delayed for at least 6–12 months in some patients.

Chondral defect characteristics also determine suitability for ACI. Patients with symptomatic grade III or IV focal defects of the femoral condyles, trochlea and patella are potential candidates for ACI.[3] It is important that defect location on arthroscopy or imaging correlates with the patient's symptoms. Defects under 2 cm^2 are generally best treated with microfracture or osteochondral autograft transplantation with consideration of ACI as second-line management in patients with poor outcomes. ACI has been used to resurface defects of up to 26.6 cm^2[25]; however, many recommend lesions between 2 and 10 cm^2[22] or 2 and 12 cm^2[23] to be considered for ACI. Patients should also have bone loss of less than 6–8 mm^2; however, simultaneous or staged bone grafting can be performed if required.[6] Patients with over 50% joint space narrowing and bipolar disease are less likely to benefit from ACI.[3] Recipricol or 'kissing' lesions are commonly cited as a contraindication to ACI.[1] ACI is contraindicated in patients with active inflammatory arthritis or infection.[7]

Careful evaluation for coexistant patello-femoral malalignment, ligamentous instability or meniscal pathology is important. Poor results were initially reported for patellofemoral lesions treated with ACI[8]; however, with recognition of the importance of patello-femoral malalignment, results have improved. Multiple series have since reported on realignment procedures such as anterormedialization being performed with patello-femoral ACI as a combined procedure, and results have been very encouraging. Outcomes are now approaching those for condylar lesions.[9–12] ACI can also be performed in conjunction with meniscus transplantation in a meniscal-deficient knee to facilitate improved biomechanics. In addition, high tibial or distal femoral osteotomy is liberally recommended for coronal plane malalignment when treating tibio-femoral lesions in the relevant compartments.

Operative technique

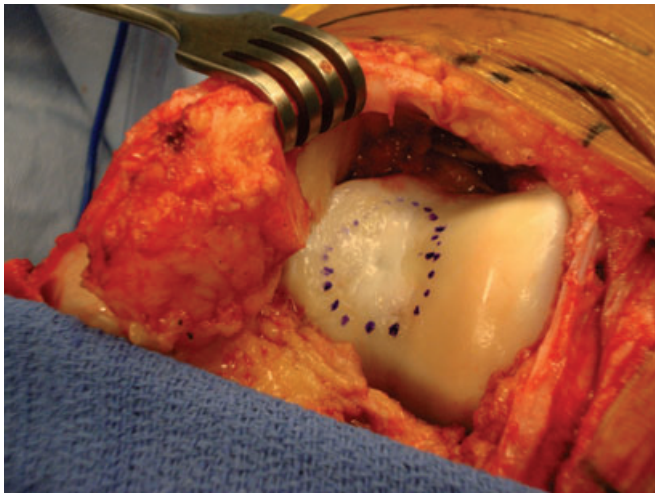
ACI is a two-stage surgical procedure, first performed on human knees by Brittberg *et al*.,[8] involving a cartilage harvest followed by implantation of cultured autologous chondrocytes. The surgical procedure and its refinements have been described in several articles since its development.[3,12–16]

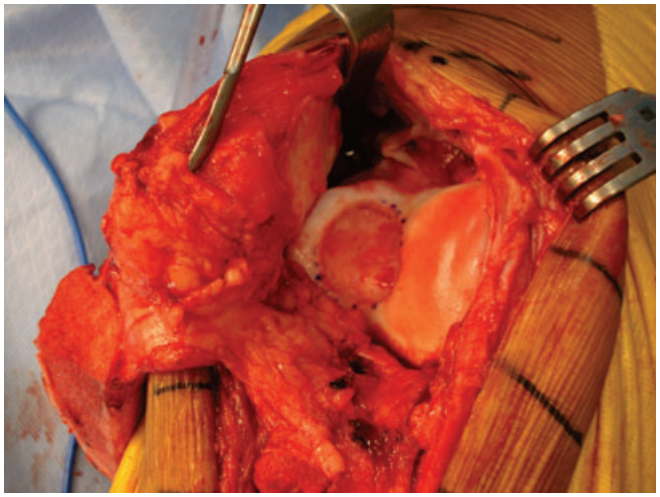
The first stage of the procedure is an arthroscopic assessment of the joint and cartilage biopsy. The size and depth of the chondral lesion and the quality and thickness of the surrounding articular cartilage are evaluated. Approximately 200–300 mg of articular cartilage is harvested from a non-weight-bearing region of the knee. The cartilage then undergoes enzymatic digestion in order to release cells and is cultured for between 3 and 6 weeks prior to implantation.[8,13,14,17] In the case of a matrix-induced autologous chondrocyte implantation (MACI), chondrocyte cells are incorporated into a type-I/III collagen scaffold during the culturing process.[6,13]

The second stage involves implantation of the cultured chondrocytes. It requires surgical debridement of the defect to healthy articular tissue around its edge and subchondral bone at its base (Figs. 1 and 2).[2,14] Care is taken to avoid penetration of the subchondral plate to avoid contamination of the defect by bone marrow tissue, which is believed to increase the risk of fibrocartilage formation.[14] If bleeding does occur, an adrenaline-soaked swab can be used to obtain haemostasis.[2,18] Alternatively, fibrin glue can be applied to the surface during the suturing of the periosteal flap.

The next step varies depending on the type of ACI procedure being performed. The original ACI technique involves a periosteal flap being sewn over the defect, under which a suspension of cultured chondrocytes is injected (ACI-P).[2,8,13] Typically, the periosteal flap is harvested from the proximal-medial part of the tibia and should be at least 2 mm larger than the defect.[3] Alternatively, synthetic collagen-membranes have been used as a substitute for the periosteal patch (ACI-C).[2] Collagen-membranes are thought to be advantageous because of decreased surgical exposure, reduced operating time and a reduction in the complications related to periosteal flap use, including graft hypertrophy.[2,6,13,18] The periosteal flap or collagen-membrane is sutured in an interrupted fashion over the chondral defect using 6-0 Vicryl (polyglactin; Ethicon Inc., Somerville, NJ, USA).[3] Sutures should be placed approximately 4 mm apart, with a small interval left at the superior most aspect to allow for chondrocyte injection (Fig. 3).[2,3] Fibrin glue is then used to seal the edges of the patch, and a 'water-tight' test may be performed.[2,3,6,14] Cultured chondrocytes are then implanted beneath the patch through the interval using an 18-gauge angiocatheter (Fig. 4). The interval is subsequently closed with suture and fibrin glue.[2]

The MACI technique has been developed amid concerns regarding the use of chondrocytes in suspension resulting in uneven distribution and possible cell leakage.[13,19] With this technique, the cultured chondrocyte cells are seeded directly onto a biodegradable porcine type I/III collagen scaffold. The membrane can be inserted directly into the defect and secured without a cover using fibrin glue.[6,13] In addition to ensuring an even distribution of chondrocytes,





Figs 1–2. The chondral defect is exposed, marked and debrided to leave a peripheral border of healthy articular cartilage and a base of subchondral bone.

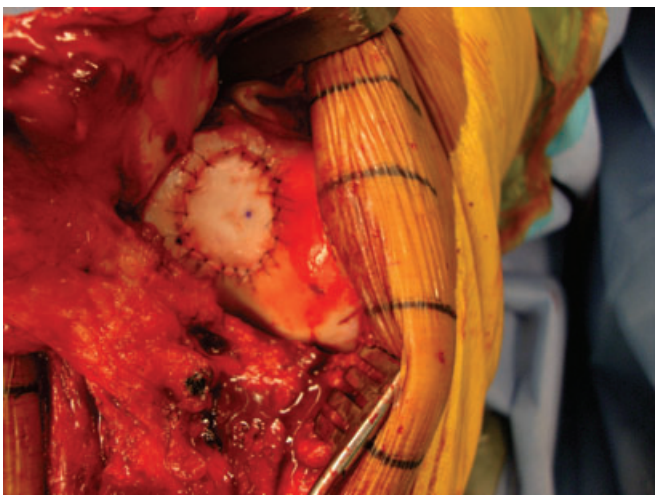


Fig. 3. The periosteal patch (or collagen membrane) is sized against the lesion, trimmed and sutured over the defect with a small interval left at the superior most aspect. Fibrin glue is used to seal the edges.

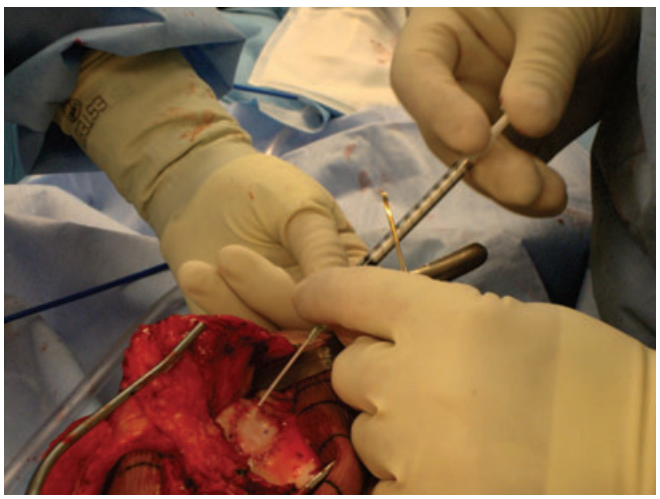


Fig. 4. Chondrocytes that have been previously harvested and cultured are injected with an angiocatheter to fill the defect beneath the patch. The interval in the patch is subsequently closed with suture and fibrin glue.

the MACI procedure may also decrease operating time and surgical exposure as it does not require sutures or periosteal harvest.[13] It has also been suggested that the scaffold may act as a barrier to fibroblast invasion, which may otherwise induce fibrous repair.[20]

Post-operative management and rehabilitation

The maturation of cartilage takes many months after implantation and has been described as having three distinct phases.[1,14] These stages help to guide patient rehabilitation and predict the time required for effective relief of symptoms.[3] There are, however, differences between rehabilitation regimes at various centres.[6]

The first phase is cellular proliferation and takes up to 6 weeks.[1,3] Initially, chondrocyte cells must adhere to the subchondral bone, a process requiring 12–18 h.[1] Many rehabilitation protocols restrict range of motion in this time frame to encourage the adherence and proliferation of cells.[1–3,6] The use of a continuous passive-motion machine commencing between 12 and 24 h post-operatively for 6–8 h a day is advocated to provide chondrogenic stimulus in the first 4–6 weeks post-operatively.[1,2,6]

The transition phase is the next in the maturation process and occurs during the next 4–6 months.[1,6,14] During this phase there is expansion of the matrix released by the chondrocytes into a putty-like consistency.[1,6] Depending on lesion size and location, weight bearing can be advanced beyond toe- or heel-touch weight bearing as early as 4 weeks post-operatively for patients with femoral condyle defects. Patients with a poorly contained lesion should restrict weight bearing for 8–12 weeks, and patients with multiple lesions will progress slower still.[1]

Patients with patellofemoral defects are permitted full weight bearing with their knee locked in extension within the first 6 weeks

post-operatively.[1] Some advocate weight-bearing activity in the days following surgery.[2] Continuous passive motion is also used but typically progress more slowly than femoral condyle lesions.[1] When a concomitant tibial tuberosity is performed, weight bearing is protected to avoid a post-operative tibial fracture from occurring.

The final matrix remodeling phase commences approximately 6 months after surgery and continues for at least 6–12 months.[1] In this phase, the cartilage tissue progressively hardens, acquiring properties similar to the adjacent healthy cartilage.[1,6] The gradual relief of preoperative symptoms occurs during this phase, and the patient may return to normal activities at 12 months post-operatively. Graft maturation, and thus symptom relief, can continue for up to 3 years post-operatively. Factors affecting cartilage maturation include physiological age, size and site of lesion, and desired final activity level.[1]

Review of outcomes

Short to medium outcome data for patients treated with ACI is currently available and overall the results are encouraging (Table 1).

Case series and cohort studies of ACI

Following promising animal model results,[21] a landmark study by Brittberg *et al*.[8] evaluated the treatment of deep cartilage defects of the femoral condyle and patella with autologous chondrocytes. The results were encouraging for patients with femoral condyle lesions; 14 of 16 patients had good to excellent results 2 years post-operatively. In the patella transplant population the results were less encouraging with good to excellent results achieved in only two of seven patients, fair results in three and poor results in two at a mean follow-up of 36 months.

In 2000, studies by Erggelet,[22] Peterson[16] and their associates also showed positive outcomes following ACI. Erggelet *et al*. 's case series of 24 patients showed improvements in the Cincinnati knee score from 3.6 preoperatively to 8.1 points at 12 months post-operatively. Peterson *et al*. 's 101 patient case series achieved good to excellent outcomes in 76.5% of patients overall, with the greatest overall outcomes in patients with isolated femoral condylar defects (92% good to excellent) and osteochondritis dissecans (89% good to excellent outcomes). Another prospective cohort study of 169 patients by Minas[23] had similarly positive outcomes with 87% of patients experiencing clinical improvement.

In 2002, Peterson *et al*.[12] released further analysis of the long-term durability of ACI within their patient population showing good to excellent outcomes in 83.6% of the 61 patients at a mean follow-up of 7.4 years. Peterson *et al*.[15] in 2003 reported on a case series looking at outcomes of patients with osteochondritis dissecans treated with ACI. Of the 58 patients included, 91% achieved a good to excellent rating on clinical evaluation after mean follow-up of 5.6 years. Significant improvement was documented using the Cincinnati (from 2.0 to 9.8, $P < 0.001$), Lysholm (from 44.3 to 92.4, $P < 0.001$), Tegner-Wallgren (from 6.3 to 10.2, $P < 0.001$) and Brittberg-Peterson visual analog scale (VAS) (from 80.2 to 26.7, $P < 0.001$) scoring systems.

In 2005, Mithofer *et al*.[24] published the results of a case series evaluating the use of ACI repair in patients with high physical demands. Forty-five competitive and recreational soccer players underwent ACI with mean follow-up of 41 months. Good to excellent outcomes were achieved in 72% of patients with overall improvement in Tegner activity score from 3.6 to 6.1 ($P < 0.001$). Results were better in patients with isolated lesions (85% good to excellent outcomes) and best in those with single defects in the medial femoral condyle (93% good to excellent rating). In the same year, Browne *et al*.[25] released results from a multi-centre prospective cohort study in the USA. There was a mean improvement of 2.6 points ($P < 0.001$) in the modified Cincinnati score for the 87 patients who completed 5-year follow-up assessments.

In 2007, studies by Steinwachs *et al*.,[26] Kreuz *et al*.[27] and Mandelabaum *et al*.[28] investigated the use of synthetic collagen membranes in ACI, the use of physical activity in rehabilitation from ACI and treatment outcomes of ACI for cartilage defects of the trochlea, respectively. Steinwachs *et al*.[26] used the International Cartilage Repair Society (ICRS) and modified Cincinnati rating systems to show significant ($P < 0.05$) improvement at all time intervals post-operatively using type I/III collagen membranes. Kreuz *et al*.[27] concluded that physical activity improves the outcome of ACI, showing significantly better results at 18 and 36 months ($P < 0.05$) in patients with regular sports involvement. Mandelbaum *et al*.[28] achieved significant improvement in pain ($P < 0.0001$), swelling ($P < 0.0001$) and overall ($P < 0.0001$) Cincinnati scores when using ACI for the treatment of full-thickness lesions of the trochlea.

Rosenberger *et al*.[29] in 2008 reported good to excellent results in 72% of patients in a case series investigating ACI in patients aged 45 years or older (mean age 48.6). They also showed significant overall improvement ($P < 0.001$) in Short Form 36 (SF-36) Health Survey, Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index, Knee Society Score (KSS) and Cincinnati scores.

In 2009, Zaslav *et al*.[4] published a prospective multi-centre cohort study evaluating the effectiveness of ACI in patients with failed prior treatments for articular cartilage defects. Of the 126 patients, 82% completed the 48-month follow-up, and of these, 76% were deemed treatment successes. Significant ($P < 0.001$) improvements were observed from baseline to all time points on the International Knee Documentation Committee (KOOS), Cincinnati, VAS and SF-36 scoring systems for all outcome measures.

Most recently, McNickle *et al*.[5] reported significant mean improvement in all outcome assessments including Lysholm (41–69, $P < 0.001$) and International Knee Documentation Committee (IKDC) (34–64, $P < 0.001$) scales in a study of 137 patients (140 knees) with full-thickness articular cartilage defects refractory to prior treatments at a mean follow-up of 4.3 years. The study also identified age and worker's compensation status as independent predictors of outcome.

Comparison of ACI with other cartilage restoration techniques.

Numerous studies have directly compared ACI with other methods for the treatment of articular cartilage lesions including microfracture, osteochondral grafting procedures and arthroscopic debridement (Table 2).

Table 1 Outcomes for case series of autologous chondrocyte implantation

Author	*n*	Patient population	Mean age (range)	Mean lesion size cm^2 (range)	Lesion location	Mean follow up (range)	Principle outcomes
McNickle *et al.*[5]	137	Symptomatic, full thickness defects refractory to prior treatment.	30.3 (13.9–49.9)	5.2 (0.8–26.6)	62 MFC, 24 LFC,13 Tr, 41 Pat	4.3 years (2–9.7)	Improvement in Lysholm (41 to 69, $P < 0.001$) and IKDC scores (34 to 64, $P < 0.001$). Age and workers compensation independent predictors of outcome.
Zaslav *et al.*[4]	154	Failed treatment for articular cartilage defects within the last 3 years.	34.5 (>18), S.D. 8.1	4.63 (1–30), S.D. 3.2	102 MFC, 27 LFC, 24 Tr	45.3 months	Improvements from baseline to all time points for KOOS, Cincinnati, VAS and SF-36 scores ($P < 0.001$)
Rosenberger *et al.*[29]	56	Patients over 45 years with full thickness chondral defects.	48.6 (45–60)	4.7 (1–15)	46 MFC, 11 LFC, 34 Tr, 26 Pat, 1 MTP, 1 LTP	4.7 years (2–11)	Good/excellent results in 72%. 14% failure rate. Improvements in SF-36 (48.9 to 57.2, $P < 0.001$), WOMAC (56.6 to 38.3, $P < 0.001$), Cincinnati (3.6 to 5.9, $P < 0.001$), KSS (60.4 to 82.7, $P < 0.001$).
Kreuz *et al.*[27]	118	Symptomatic, isolated chondral lesions in sporting and non-sporting patients.	35 (18–50)	6.5 (3–16)	78 MFC or LFC, 17 Tr, 23 Pat.	3 years	Significantly more improvement in ICRS and Cincinnati scores in sporting patient group at 18 ($P < 0.05$) and 36 months ($P < 0.05$).
Mandelbaum *et al.*[28]	40	Cartilage repair registry patients with moderate to large isolated troclea lesions.	37 (16–48)	4.5 (1–14)	40 Tr	59 months (24–84), S.D.18 months	Cincinnati scores improved for; overall condition 3.1 to 6.4 ($P < 0.0001$), pain 2.6 to 6.2 ($P < 0.0001$) and swelling 3.9 to 6.3 ($P < 0.0001$).
Steinwachs *et al.*[26]	63	Full thickness chondral lesions.	34.3 (18–50)	5.85 (3–16)	34 MFC or LFC, 10 Tr, 19 retro-Pat	3 years	Improvement in modified Cincinnati score and ICRS at 6, 18 and 36 months ($P < 0.01$). No difference in outcome based on defect location ($P > 0.2$).
Browne *et al.*[25]	100	Cartilage repair registry patients with unilateral full thickness femoral condyle lesions.	37 (14–55)	4.9 (0.84–23.54)	81 MFC, 18 LFC, 17 Tr	5 years	Mean improvement in modified Cincinnati score of 2.6 points (<0.0001). For the 62 patients who improved, average improvement of 4.1 points ($P < 0.0001$).
Mithofer *et al.*[24]	45	Competitive and recreational soccer players with full-thickness defects.	26 (14–43)	5.7	19 MFC, 10 LFC, 2 Tr, 1 Pat	41 months (12–108)	Good/excellent results in 72%. Tegner activity score improved 3.6 to 6.1 ($P < 0.001$). 33% returned to soccer, including 83% of competitive players.
Peterson *et al.*[15]	58	Osteochondritis dissecans, 48 with prior operations.	26.4 (14–52)	5.7 (1.5–12)	39 MFC, 19 LFC	5.6 years (1–10)	Good/excellent results in 91%. Improvements in; Cincinnati (2.0 to 9.8, $P < 0.001$). Lysholm (44.3 to 92.4, $P < 0.001$), Tegner-Wallgren (6.3 to 10.2, $P < 0.001$) and Brittberg-Peterson VAS scores (80.2 to 26.7 $P < 0.001$)
Peterson *et al.*[12]	61	Isolated, symptomatic, full thickness defects of femoral condyle or patella.	28.4	4.11 (1.3–12)	44 Femoral Condyle, 17 Pat	7.4 years (5–11)	Good/excellent results in 83.6%. Significant improvement in all sub-groups (Tegner-Wallgren, Cincinnati, Lysholm, Brittberg-Peterson VAS scores).
Minas *et al.*[23]	169	Diverse patient population; isolated/ multiple femoral condyle defects, patients with arthritic changes.	36.2 (13–58)	7.31	127 MFC, 37 LFC, 76 Tr, 43 Pat, 12 TP	(12 to 24 months)	Clinical improvement in 87%. Statistically significant improvement in all subgroups using KSS.
Peterson *et al.*[16]	101	Symptomatic, full thickness chondral defects of femoral condyle or patella.	29.4 (15–51)	4.38 (1.3–12)	57 Femoral Condyle, 19 Pat, 18 Other	(2–9 years)	Good/excellent outcomes in 76.5% of patients using Brittberg grading score.
Erggelet *et al.*[22]	24	Grade IV cartilage lesions, 23 patients had at least 1 prior treatment.	—	6.27	—	12 months (6–24)	Improvement (3.6 to 8.1) in Cincinnati score at 12 months.
Brittberg *et al.*[8]	23	Symptomatic, full thickness, chondral lesions of femoral condyle or patella.	27 (14–48)	3.1 (1.6–6.5)	2 LFC, 14 MFC, 7 Pat	39 months (16–66)	Good/excellent outcomes in 87.5% of femoral condyle patients. 28.6% of patella patients had good/excellent outcomes, 42.9% fair, 28.6% poor.

KOOS, Knee Injury and Osteoarthritis Outcome Score; IKDC, International Knee Documentation Committee; MFC, Medial femoral condyle; LFC, Lateral femoral condyle; VAS, visual analog scale; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index; SF-36, SF36 Health Survey; KSS , Knee Society Score; Tr, Trochlea; Pat, Patella; MTP, Medial Tibial plateau; LTP, Lateral Tibial Plateau; ICRS, International Cartilage Repair Society; TP, Tibial plateau.

Table 2 Outcomes for autologous chondrocyte implantation comparative studies

Author	Study design	*n*, ACI	*n*, group 2	Patient population	Mean age (range)	Mean lesion size cm^2 (range)	Lesion location	Mean follow-up (range)	Principle outcomes
Kon *et al.*[32]	Cohort Study	40	40, MFX	Grade III or IV femoral condyle or trochlea lesions	29.8	2.4 (1.4–4.4)	MFX: 28 MFC, 10 LFC, 2 Tr.ACI: 26 MFC, 12 LFC, 2 Tr.	5 years	Improvement in both groups using IKDC ($P < 0.001$). Better results for ACI group in IKDC objective score (15% normal/nearly normal to 90%, $P < 0.001$) and subjective score (40.5 to 80.2, $P = 0.003$).
Saris *et al.*[31]	RCT	57	61, MFX	Single symptomatic grade III or IV lesions between 1–5 cm of femoral condyle	33.9 (18–50)	2.5	118 MFC/LFC	18 months	Similar improvement in KOOS score from 56.3 to 74.7 for MFX, 59.5 to 75.0 for ACI. Better structural repair for ACI as assessed by histomorphometry ($P = 0.003$) and overall histological evaluation ($P = 0.012$).
Knutsen *et al.*[30]	RCT	40	40, MFX	Single chronic symptomatic lesion of femoral condyle	32.2	4.8 (2–10)	71 MFC, 9 LFC	5 years	In both groups: satisfactory results in 77%, younger patients had better outcomes. No significant difference in clinical and radiographic results between groups and no correlation between histological findings and clinical outcome.
Dozin *et al.*[33]	RCT	22	25, Mosaicplasty	Symptomatic grade III or IV focal femoral condyle/ patella lesions without subchondral bone loss or prior treatment.	28.7 (16–40)	1.9	ACI: 14 MFC, 2 LFC, 6 Pat. Mosaicplasty: 12 MFC, 3 LFC, 7 Pat.	291 days (0–1339)	14 (30%) had substantial improvement with debridement negating need for further treatment. Lysholm knee score of 90–100 was observed in 88% mosaicplasty and 68% of ACI at follow-up ($P = 0.093$). Only 52.3% of patients were followed up.
Fu *et al.*[34]	Retrospective Cohort	58	58, Arthos. Debrid.	Cartilage repair registry patients. Symptomatic grade III or IV chondral defects of femoral condyles or trochlea.	36.9	4.75	ACI: 45 MFC, 8 LFC, 5 Tr. Debridement: 35 MFC, 12 LFC, 4 Tr., 7 Other	3 years min.	Median overall condition ($P < 0.01$), pain ($P < 0.01$) and swelling scores ($P < 0.05$) higher for ACI (Modified Cincinnati scale). Overall score improvement 81% for ACI and 60% for debridement ($P < 0.05$). Of patients who improved, median was 5 points ACI versus 2 points debridement ($P < 0.001$).
Bentley *et al.*[17]	RCT	58	42, MOA	Symptomatic cartilage lesion	31.3 (16–49)	4.66 (1.0–12.2)	53 MFC, 18 LFC, 25 Pat., 3 Tr., 1 LTC.	19 months (12–26)	Good/excellent outcomes in 88% of ACI group vs 69% of MOA group ($P = 0.277$). For MFC subgroup 88% good/excellent for ACI group versus 74% MOA group ($P = 0.032$).
Horas *et al.*[35]	RCT	20	20, Osteochondral Autografts	Symptomatic single lesion extending through cartilage tidemark on femoral condyle	33.4 (18–44)	3.75 (3.2–5.6)	ACI: 16 MFC, 3 LFC, 1 MFC and Pat. OA: 16 MFC, 4 LFC	2 years	Improvement for both groups (Lysholm, Meyers and Tegner Scores). Slower recovery for ACI group at 6, 12 and 24 months ($P < 0.015$) (Lysholm Score). No significant difference between groups in Meyers/Tegner scores.

MFX, Microfracture; ACI, Autologous Chondrocyte Implantation; IKDC, International Knee Documentation Committee; RCT, Randomised Control Trial; MFC, Medial Femoral Condyle; LFC, Lateral Femoral Condyle; KOOS, Knee Injury and Osteoarthritis Outcome Score; Pat, Patella; Tr, Trochlea; MOA, Mosaicplasty; LTC, Lateral tibial condyle; OA, Osteochondral Autografts.

ACI versus microfracture

In 2007, Knutsen *et al*.[30] randomized 80 patients with a single symptomatic cartilage defect of the femoral condyle to treatment with ACI or microfracture who were reviewed at 2 and 5 years. Both groups had significant improvement in mean Lysholm and Visual Analogue Pain Scales at final follow-up ($P < 0.05$); however, there was no significant difference between groups in terms of clinical or radiological outcomes. In a similar series investigating patients with single symptomatic grade III to IV cartilage lesions on the femoral condyles, Saris *et al*.[31] randomized patients to ACI or microfracture. Patients were evaluated at 12 and 18 months post-operatively for histological and clinical outcomes. ACI was associated with better structural repair as measured by histomorphology ($P = 0.003$) and overall histologic evaluation ($P = 0.012$); however, short-term clinical outcomes were similar for both groups. Kon *et al*.[32] recently published further results comparing a MACI to microfracture. Eighty patients were randomized to each treatment group and followed for 5 years. Similar to the Knutsen and Saris studies, both groups showed significant improvement in clinical outcomes at follow-up; however, Kon demonstrated greater improvement in the International Knee Documentation Committee objective ($P < 0.001$) and subjective ($P < 0.003$) scores for the MACI group compared with those treated with microfracture.

ACI versus mosaicplasty

Bentley and associates[17] conducted a randomized comparison of ACI to mosaicplasty for patients with symptomatic articular cartilage lesions of the knee. Patients were followed for an average of 19 months and assessed using modified Cincinnati and Stanmore scores. Good or excellent results were found in 88% of ACI patients and 69% of mosaicplasty patients; however, the difference was not significant ($P = 0.277$). For lesions on the medial femoral condyle, however, ACI produced significantly better outcomes (88% good/excellent versus 74% good/excellent, $P < 0.032$). At follow-up arthroscopy, significantly better repairs were seen in the ACI group (82% good/excellent versus 34% good/excellent, $P < 0.01$), and the authors concluded that ACI is superior to mosaicplasty for the repair of articular cartilage defects of the knee. In another randomized trial comparing ACI with mosaicplasty published by Dozin *et al*.,[33] 47 patients underwent an initial arthroscopic debridement at the time of enrolment and had the assigned treatment scheduled 6 months later. Interestingly, 31.8% ($n = 14$) of patients were asymptomatic enough at the 6-month mark to warrant no further treatment. Among the other patients, 88% of the mosaicplasty and 68% of the ACI patients obtained a complete recovery ($P = 0.093$).

ACI versus arthroscopic debridement

In a retrospective cohort study using registry data, 58 ACI patients and 58 debridement patients were compared by Fu *et al*.[34] Patients were similar in terms of baseline characteristics; however, at follow-up a minimum of 3 years later, 81% of the ACI group and 60% of the debridement group had improved ($P < 0.05$). Of these patients, the median improvement was significantly better in the ACI group (5 points ACI versus 2 points Debridement, $P < 0.001$).

Conclusions

ACI represents a promising treatment modality in the surgical management of articular cartilage defects when used judiciously in carefully selected patients. Short to medium-term results reported to date have shown largely positive outcomes, and long-term follow-up is eagerly awaited.

Conflict of interest

Brian Cole, MD, MBA: Consultant for Genzyme Tissue Repair, Cambridge, MA.

References

1. Jones DG, Peterson L. Autologous chondrocyte implantation. *J. Bone Joint Surg. Am.* 2006; **88**: 2502–20.
2. Cole BJ, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. *J. Bone Joint Surg. Am.* 2009; **91**: 1778–90.
3. King PJ, Bryant T, Minas T. Autologous chondrocyte implantation for chondral defects of the knee: indications and technique. *J. Knee Surg.* 2002; **15**: 177–84.
4. Zaslav K, Cole B, Brewster R *et al*. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am. J. Sports Med.* 2009; **37**: 42–55.
5. McNickle AG, L'Heureux DR, Yanke AB, Cole BJ. Outcomes of autologous chondrocyte implantation in a diverse patient population. *Am. J. Sports Med.* 2009; **37**: 1344–50.
6. Gikas PD, Bayliss L, Bentley G, Briggs TWR. An overview of autologous chondrocyte implantation. *J. Bone Joint Surg .Br.* 2009; **91**: 997–1006.
7. Gillogly SD. Treatment of large full-thickness chondral defects of the knee with autologous chondrocyte implantation. *Arthroscopy* 2003; **19**(Suppl. 1): 147–53.
8. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N. Engl. J. Med.* 1994; **331**: 889–95.
9. Farr J, 2nd. Autologous chondrocyte implantation and anteromedialization in the treatment of patellofemoral chondrosis. *Orthop. Clin. North Am.* 2008; **39**: 329–35.
10. Henderson IJP, Lavigne P. Periosteal autologous chondrocyte implantation for patellar chondral defect in patients with normal and abnormal patellar tracking. *Knee* 2006; **13**: 274–9.
11. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. *Clin. Orthop.* 2005; 30–9.
12. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *Am. J. Sports Med.* 2002; **30**: 2–12.
13. Bartlett W, Skinner JA, Gooding CR *et al*. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J. Bone Joint Surg. Br.* 2005; **87**: 640–5.
14. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin. Sports Med.* 1999; **18**: 13–44.
15. Peterson L, Minas T, Brittberg M, Lindahl A. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J. Bone Joint Surg. Am.* 2003; **85-A**(Suppl. 2): 17–24.

16. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin. Orthop.* 2000; **374**: 212–34.
17. Bentley G, Biant LC, Carrington RWJ *et al*. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J. Bone Joint Surg. Br.* 2003; **85**: 223–30.
18. Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: periosteum covered versus type I/III collagen covered. *Knee* 2006; **13**: 203–10.
19. Sohn DH, Lottman LM, Lum LY *et al*. Effect of gravity on localization of chondrocytes implanted in cartilage defects. *Clin. Orthop.* 2002; 254–62.
20. Frenkel SR, Toolan B, Menche D, Pitman MI, Pachence JM. Chondrocyte transplantation using a collagen bilayer matrix for cartilage repair. *J. Bone Joint Surg. Br.* 1997; **79**: 831–6.
21. Bentley G, Greer RB, 3rd. Homotransplantation of isolated epiphyseal and articular cartilage chondrocytes into joint surfaces of rabbits. *Nature* 1971; **230**: 385–8.
22. Erggelet C, Steinwachs MR, Reichelt A. The operative treatment of full thickness cartilage defects in the knee joint with autologous chondrocyte transplantation. *Saudi Med. J.* 2000; **21**: 715–21.
23. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin. Orthop.* 2001; **391S**: S349–61.
24. Mithofer K, Peterson L, Mandelbaum BR, Minas T. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. *Am. J. Sports Med.* 2005; **33**: 1639–46.
25. Browne JE, Anderson AF, Arciero R *et al*. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. *Clin. Orthop.* 2005; **436**: 237–45.
26. Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up. *Arthroscopy* 2007; **23**: 381–7.
27. Kreuz PC, Steinwachs M, Erggelet C *et al*. Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. *Am. J. Sports Med.* 2007; **35**: 1261–8.
28. Mandelbaum B, Browne JE, Fu F *et al*. Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. *Am. J. Sports Med.* 2007; **35**: 915–21.
29. Rosenberger RE, Gomoll AH, Bryant T, Minas T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. *Am. J. Sports Med.* 2008; **36**: 2336–44.
30. Knutsen G, Drogset JO, Engebretsen L *et al*. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J. Bone Joint Surg. Am.* 2007; **89**: 2105–12.
31. Saris DBF, Vanlauwe J, Victor J *et al*. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am. J. Sports Med.* 2008; **36**: 235–46.
32. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M. Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. *Am. J. Sports Med.* 2009; **37**: 33–41.
33. Dozin B, Malpeli M, Cancedda R *et al*. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin. J. Sport Med.* 2005; **15**: 220–6.
34. Fu FH, Zurakowski D, Browne JE *et al*. Autologous chondrocyte implantation versus debridement for treatment of full-thickness chondral defects of the knee: an observational cohort study with 3-year follow-up. *Am. J. Sports Med.* 2005; **33**: 1658–66.
35. Horas U, Pelinkovic D, Herr G *et al*. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. *J Bone Joint Surg Am.* 2003; **85-A**: 185–92.