Autologous chondrocyte implantation *versus* matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee

A PROSPECTIVE, RANDOMISED STUDY

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Autologous chondrocyte implantation (ACI) is used widely as a treatment for symptomatic chondral and osteochondral defects of the knee. Variations of the original periosteum-cover technique include the use of porcine-derived type I/type III collagen as a cover (ACI-C) and matrix-induced autologous chondrocyte implantation (MACI) using a collagen bilayer seeded with chondrocytes. We have performed a prospective, randomised comparison of ACI-C and MACI for the treatment of symptomatic chondral defects of the knee in 91 patients, of whom 44 received ACI-C and 47 MACI grafts.

Both treatments resulted in improvement of the clinical score after one year. The mean modified Cincinnati knee score increased by 17.6 in the ACI-C group and 19.6 in the MACI group (p = 0.32). Arthroscopic assessments performed after one year showed a good to excellent International Cartilage Repair Society score in 79.2% of ACI-C and 66.6% of MACI grafts. Hyaline-like cartilage or hyaline-like cartilage with fibrocartilage was found in the biopsies of 43.9% of the ACI-C and 36.4% of the MACI grafts after one year. The rate of hypertrophy of the graft was 9% (4 of 44) in the ACI-C group and 6% (3 of 47) in the MACI group. The frequency of re-operation was 9% in each group.

We conclude that the clinical, arthroscopic and histological outcomes are comparable for both ACI-C and MACI. While MACI is technically attractive, further long-term studies are required before the technique is widely adopted.

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Autologous chondrocyte implantation (ACI) has undergone considerable development since its inception more than 15 years ago.[1] It has become an established form of treatment for symptomatic osteochondral defects in the knee[2-7] and has recently been adapted for use in the shoulder, elbow and ankle.[8-10]

The original ACI technique involved the injection of a suspension of cultured chondrocytes into a debrided chondral defect beneath a periosteal cover (ACI-P).[1] Periosteum was the favoured cover material since it was thought to have a chondrogenic action, either by providing growth factors or mesenchymal stem cells with the potential to develop into chondrocytes.[2,11] There have, however, been complications associated with the use of periosteum as a cover material, including hypertrophy of the graft and, less commonly, calcification and delamination.[2,6,7,12] The harvesting of periosteum also increases the operating time and requires a larger surgical exposure, which may be associated with increased pain and arthrofibrosis.[13] These disadvantages have led to the development of bio-absorbable covers as an alternative. Initial studies on the use of a cover manufactured from porcine-derived type I/type III collagen (ACI-C), have reported a similar clinical outcome to that of ACI-P, although with a lower incidence of hypertrophy of the graft.[3,4,14]

The implantation of cultured chondrocytes in suspension, as is used for both ACI-P and ACI-C, has led to concerns about the uneven distribution of chondrocytes within the defect and the potential for cell leakage.[15] In order to overcome such problems, biodegradable scaffolds seeded with chondrocytes have been developed. A further advantage of this method of cell delivery is that the scaffold may act as a barrier to invasion of the graft by fibroblasts, which may otherwise induce fibrous repair.[16] One approach has been to implant chondrocyte cells on a membrane, using the matrix-induced autologous chondrocyte implantation (MACI) technique (Verigen, Leverkusen, Germany).[9] The MACI membrane consists of a porcine type I/type III collagen bilayer seeded with chondrocytes. One surface has a roughened appearance because of widely-spaced col-

lagen fibres, between which chondrocytes are seeded. The other side has a smooth surface due to a higher density of collagen fibres.[17] The MACI membrane can be secured directly to the base of a prepared chondral defect by fibrin glue and without a cover. Because MACI implantation is suture-free and does not require periosteal harvesting, the procedure may be performed faster and with a less extensive exposure.

We have used the MACI technique for more than two years, and have five years of experience with the ACI-C method. Our study, therefore, compares the clinical, arthroscopic and histological outcomes of osteochondral defects in the knee treated by ACI-C or MACI in a randomised trial.

Patients and Methods

The study was approved by the Joint Research and Ethics committee of the Royal National Orthopaedic Hospital Trust. The primary indication for surgery was persistent pain which was attributable to a lesion of the articular cartilage. The inclusion criteria were between 15 and 50 years of age, an isolated osteochondral defect larger than 1 cm^2, and the ability to follow the rehabilitation programme. Lesions smaller than 1 cm^2 were treated by marrow-stimulation techniques. Joint instability, malalignment and bone deficiency required correction either before or at the time of implantation of cartilage. Patients with osteoarthritis and inflammatory joint disease were excluded.

Between 22 February 2002 and 11 April 2003, 107 patients underwent ACI for isolated, symptomatic osteochondral defects in the knee. They were treated in one hospital by three different surgeons (JAS, RWJC, GB). Sixteen patients underwent MACI without randomisation, and have therefore been excluded from the study. The excluded patients had either defects which were considered to be more suitable for MACI because of poor containment of the defect or difficult access (five patients) or they had undergone a combination of procedures including MACI with reconstruction of the anterior cruciate ligament (four), MACI with bone grafting of the defect (four), MACI with patellar realignment (two), and MACI with high tibial osteotomy (one). Using sealed envelopes, the remaining 91 patients were block randomised to undergo either ACI-C (44) or MACI (47).

There were 54 men and 37 women with a mean age of 33.7 years (15 to 49) in the ACI-C group and 33.4 years (17 to 47) in the MACI group. The mean duration of symptoms was 118.5 months (12 to 360) in the ACI-C and 87.9 months (9 to 356) in the MACI group. In addition to diagnostic arthroscopy, patients in the ACI-C group had undergone a mean of 2.3 previous surgical procedures to the affected knee compared with 2.1 in the MACI group.

All patients complained of pain and functional impairment. Their clinical status was graded using the modified Cincinnati knee score,[18] the Stanmore functional rating score,[19] and a visual analogue score (VAS). There were no significant differences in the pre-operative clinical scores between the groups. The mean modified Cincinnati knee score was 41.0 (10 to 66) in the ACI-C group and 44.5 (10 to 74) in the MACI group. The mean Stanmore functional rating was 3.0 in the ACI-C group and 2.7 in the MACI group. The mean visual analogue pain score was 3.0 in both groups.

Table I. Anatomical site of chondral lesions, including multiple defects, found in 91 patients, by number and *percentage*

Anatomical site	ACI-C	MACI
Medial femoral condyle	25 (*42.4*)	25 (*47.2*)
Lateral femoral condyle	5 (*8.5*)	6 (*11.3*)
Patella	20 (*33.9*)	16 (*30.2*)
Trochlea	9 (*15.2*)	6 (*11.3*)
Total	59 (*100.0*)	53 (*100.0*)

Table II. Aetiology of the lesions, by number and *percentage*

Aetiology	ACI-C	MACI
Trauma	18 (*40.9*)	21 (*44.7*)
Chondromalacia patellae	7 (*15.9*)	9 (*19.1*)
Osteochondritis dissecans	8 (*18.2*)	6 (*12.8*)
Failed ACI	3 (*6.8*)	0 (*0*)
Failed matrix support prosthesis	3 (*6.8*)	0 (*0*)
Failed mosaicplasty	3 (*6.8*)	2 (*4.3*)
Uncertain	2 (*4.6*)	9 (*19.1*)
Total	44 (*100*)	47 (*100*)

The mean size of the defect was 6.0 cm^2 (1.5 to 16) in the ACI-C group and 6.1 cm^2 (1.0 to 22) in the MACI group. Grafting of multiple defects was performed in six patients in the MACI group and in four in the ACI-C group. The anatomical distribution of lesions was similar in both groups (Table I). The aetiology of the lesions is shown in Table II.

Operative technique. An initial arthroscopy is performed in order to assess the site, size and containment of the chondral defect as well as the condition of the surrounding and opposing articular cartilage. Careful assessment for ligamentous and meniscal insufficiency is also made. If suitable, 200 to 400 mg of cartilage are harvested from the medial or lateral trochlea and 100 ml of venous blood are collected. The biopsy is placed in a transport medium and sent to the laboratory (Verigen) where it is cultured in the patient's serum.

After a period of between three and five weeks, the patient is re-admitted for the second stage of their procedure. Prophylactic antibiotics are given at the time of induction of general anaesthesia. A medial or lateral parapatellar arthrotomy is performed under tourniquet control. A scalpel is used to debride the defect back to healthy, stable articular cartilage (Fig. 1). Care is taken to avoid subchondral bone bleeding, which can be stopped with topical adrenaline if necessary. The size of the debrided lesion is templated. When performing the ACI technique, the type I/type III collagen membrane (Matricel, Herzogenrath, Ger-

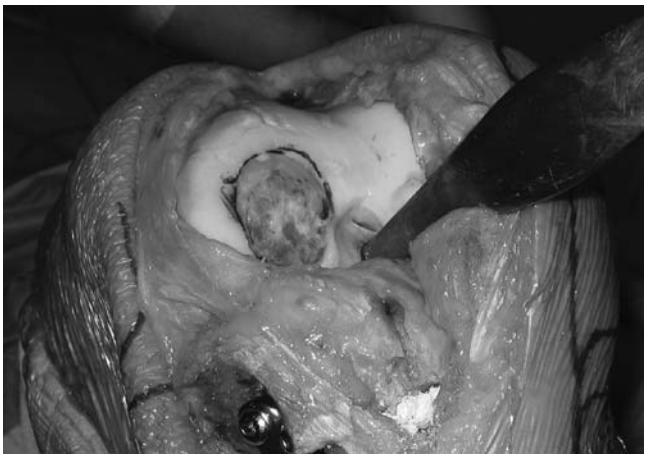

Fig. 1

Photograph of a debrided chondral lesion on the lateral femoral condyle, measuring 3 x 3 cm. The ink at the rim of the defect has been used to template the MACI membrane. The procedure has been combined with an opening-wedge high tibial osteotomy using a Pudu plate (Arthrex Ltd, East Sheffield, UK).

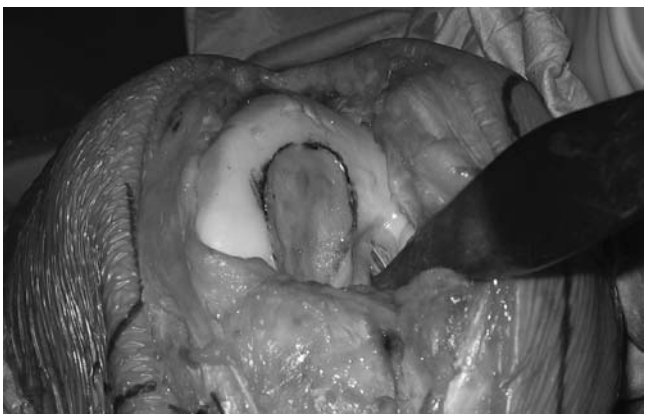

Fig. 2

Photograph showing an ACI-C membrane applied to a chondral defect on the lateral femoral condyle using 6/0 vicryl and fibrin glue. A fine catheter has been passed behind the cover to allow injection of cultured chondrocytes into the defect.

many) is cut to the appropriate size and secured to the rim of the debrided defect with 6/0 vicryl sutures spaced approximately 3 mm apart. Fibrin glue is used to ensure a water-tight seal, although a small gap at the top of the membrane is left unsutured. A fine catheter is then passed below the cover and the cultured chondrocyte suspension is injected in order to fill the defect (Fig. 2). A final suture, with additional glue, is then placed to secure the membrane.

When using MACI, fibrin glue (Tissell; Baxter, Vienna, Austria) is used to secure the membrane to the defect. The roughened side, which contains the cells, is placed face downwards (Fig. 3). Firm digital pressure is applied over the graft for three minutes while the glue sets. The stability

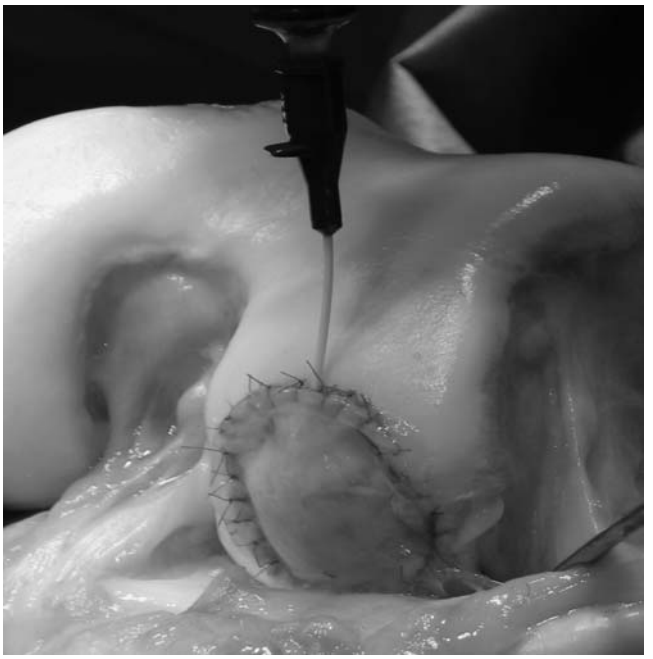

Fig. 3

Photograph showing the MACI membrane implanted over the chondral defect on the lateral femoral condyle using fibrin glue alone.

of the graft is assessed by putting the knee through a limited range of movement. If necessary, additional vicryl sutures can be used to ensure stability.

The knee is closed and held in full extension with a plaster backslab. From the first post-operative day patients are encouraged to bear weight with the aid of crutches. After two or three days, the backslab is converted to a lightweight cylinder cast and the patient is discharged from hospital. After ten days the cast is removed and the patient begins a supervised regime of physiotherapy.

After surgery patients were reviewed in the clinic at ten days, six and 12 weeks, six months, and then twice yearly. Arthroscopy was scheduled at one year after surgery. Repair of the graft was assessed using the International Cartilage Repair Society[20] criteria for cartilage repair and firmness to probing. When possible, a biopsy was taken from the centre of the graft using a Jamshidi needle of 2.5 mm in diameter (Allegiance Healthcare, Swindon, UK). An earlier arthroscopy was performed if patients developed mechanical symptoms which suggested hypertrophy or delamination of the graft.

Statistical analysis. Clinical and arthroscopic assessments performed both pre-operatively and after one year were compared using paired and unpaired *t*-tests. The level of significance was set at $p < 0.05$.

Results

At one year, the mean modified Cincinnati knee score had improved compared with pre-operative values in both

Table III. Clinical outcomes one year after both ACI-C and MACI, by number and *percentage*

Modified Cincinnati knee score[18]	ACI-C (n = 44)	MACI (n = 47)
Excellent (> 80)	10 (*22.7*)	15 (*31.9*)
Good (55 to 79)	16 (*36.4*)	19 (*40.4*)
Fair (30 to 54)	10 (*22.7*)	7 (*14.9*)
Poor (< 30)	8 (*18.2*)	6 (*12.8*)
Mean score	59.0	64.1

Table IV. Clinical outcome, as assessed by the modified Cincinnati knee score,[18] at one year after ACI-C and MACI, according to the anatomical site of the defect, by number and *percentage*

Anatomical distribution	Excellent	Good	Fair	Poor	p value
Medial femoral condyle					
ACI-C	5 (*20.8*)	8 (*33.3*)	6 (*25.0*)	5 (*20.8*)	0.62
MACI	4 (*19.0*)	11 (*52.0*)	3 (*14.0*)	3 (*14.0*)	
Lateral femoral condyle					
ACI-C	0	1 (*50.0*)	0	1 (*50.0*)	0.31
MACI	3 (*100*)	0	0	0	
Patella					
ACI-C	0	6 (*54.5*)	4 (*36.4*)	1 (*9.1*)	0.42
MACI	4 (*25.0*)	6 (*37.5*)	4 (*25.0*)	2 (*12.5*)	
Trochlea					
ACI-C	3 (*100*)	0	0	0	0.72
MACI	1 (*100*)	0	0	0	
Multiple defects					
ACI-C	2 (*50.0*)	1 (*25.0*)	0	1 (*25.0*)	
MACI	3 (*50.0*)	3 (*50.0*)	0	0	0.30

Table V. ICRS grade[20] of cartilage repair one year after ACI-C and MACI, by number and *percentage*

ICRS* grade	ACI-C	MACI
1 (excellent)	4 (*16.7*)	4 (*22.2*)
2 (good)	15 (*62.5*)	8 (*44.4*)
3 (fair)	5 (*20.8*)	5 (*27.8*)
4 (poor)	0	1 (*5.6*)

* ICRS, International Cartilage Repair Society

Table VI. Graft histology one year after ACI-C and MACI as number and *percentage*

Type of articular cartilage	ACI-C	MACI
Hyaline-like	4 (*28.6*)	3 (*27.3*)
Mixed hyaline/fibrocartilage	2 (*14.3*)	1 (*9.1*)
Fibrocartilage	8 (*57.1*)	7 (*63.6*)

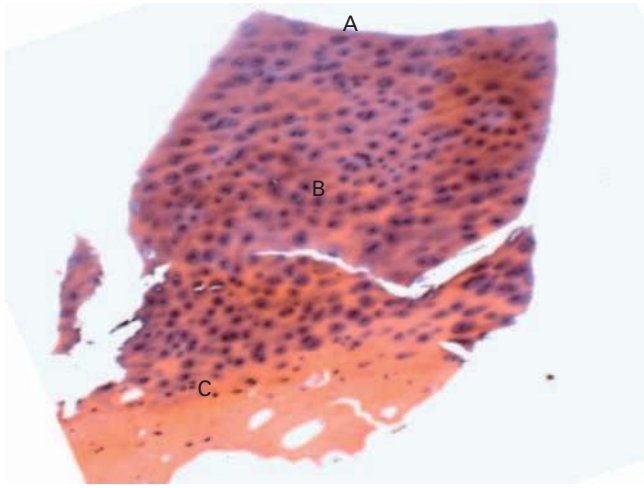

Fig. 4

Photomicrograph of an MACI graft biopsy taken one year after implantation. The surface (A) is smooth and the cartilage below (B) has a hyaline-like morphology. The tidemark (C) at the junction between the deep zone of cartilage and subchondral bone is well defined, reflecting good integration of the graft into the defect. The large cleft is a preparation artefact (haematoxylin and eosin, x4).

groups (ACI-C, 41.4 to 59.0, p = 0.01; MACI, 44.5 to 64.1, p = 0.002). The increase in the mean score was greater in the MACI than in the ACI-C group, although the difference was not statistically significant (17.5 *vs* 19.6, p = 0.32). The outcome was good or excellent in 59.1% of ACI-C patients and 72.3% of MACI patients (Table III). The mean VAS was lower after surgery in both groups (ACI-C, 6.0 to 4.3, p = 0.001; MACI, 6.0 to 4.1, p = 0.003). The Stanmore functional rating score was also reduced in both groups after surgery, representing improvement. The mean Stanmore score for the ACI-C group fell from 3.0 to 2.2 (p = 0.02) and for the MACI group from 2.7 to 2.1 (p = 0.02). The changes to both the Stanmore functional rating and VAS were not significantly different in the two groups.

The clinical outcome scores were not significantly different in the two groups when considered by anatomical site (Table IV).

A number of features were identified which conferred a worse prognosis. All patients who had undergone a revision cartilage repair after a failed mosaicplasty, ACI or carbon fibre grafting, had a poor clinical outcome, with a mean post-operative modified Cincinnati knee score of 35. A history of more than two earlier surgical procedures to the knee was associated with a worse clinical outcome, although this correlation was not statistically significant (p = 0.17). The duration of symptoms was another important prognostic factor. The mean modified Cincinnati knee score in patients with symptoms which had been present for less than 50 months was 70.1 compared with 55.8 for those with symptoms for longer than this (p = 0.004). The clinical outcome was even better in the group of seven patients who had been treated within one year (mean post-operative modified Cincinnati knee score 79.1). Patients aged less than 35 years had a significantly better clinical outcome compared with those aged more than 35 years (67.0 *vs* 56.1, p = 0.03). Patients who had been treated for lesions larger than 5 cm^2 in size had poorer clinical outcomes than those with smaller lesions, although the differences were not statistically significant (p = 0.86).

Arthroscopy was performed at one year on 24 of the patients in the ACI-C and 18 in the MACI group. The International Cartilage Repair Society score[20] was 1 (excellent)

or 2 (good) in 79.2% of ACI-C and 66.6% of MACI grafts (p = 0.3; Table V). Diagnostic histology was obtained from the biopsies of 14 ACI-C and 11 MACI patients (Table VI). The biopsies were stained with haematoxylin and eosin (Fig. 4) and Safranin O. The ACI-C group showed hyaline-like cartilage or mixed hyaline-like and fibrocartilage in 42.9% of biopsies compared with 36.4% of MACI biopsies. The frequency of hyaline-like cartilage or hyaline with fibrocartilage was not statistically different in the two groups.

The rate of graft-related complications was low. One patient from the ACI-C group developed symptoms of painful catching nine months later secondary to hypertrophy of the graft. A further three cases of hypertrophy were diagnosed in the ACI-C group at the one-year arthroscopy. In the MACI group, one patient developed symptomatic graft hypertrophy after six months which was treated by arthroscopic debridement. A further two patients in the MACI group developed hypertrophy of the graft which was debrided at the one-year arthroscopy. There were no graft failures in the ACI-C group. Two grafts failed in the MACI group, diagnosed at the one-year arthroscopy. They were located on the medial femoral condyle and patella respectively. Manipulation of the knee under anaesthesia was required for three patients in each group, and one patient in the MACI group developed a superficial wound infection. However, there were no significant general complications in any of our patients.

Discussion

We believe that this is the first randomised study which has compared ACI-C and MACI techniques for the treatment of symptomatic defects of the articular cartilage in the knee. Our study also contributes significantly to current knowledge of preliminary outcomes after MACI.

Treatment by both ACI-C and MACI resulted in significant improvements to the clinical score within one year. The frequency of good to excellent functional outcomes was higher for MACI than for ACI-C. However, improvements to the modified Cincinnati knee score, the VAS and the Stanmore functional score were not significantly different between the two techniques.

There was no significant difference between the arthroscopic appearance of the graft and the histological findings after both ACI-C and MACI. Hyaline-like cartilage or hyaline-like cartilage with fibrocartilage was present in six of 14 (42.9%) ACI graft biopsies and four of 11 (36.4%) MACI biopsies. The frequency of hyaline repair was therefore less in our study than in earlier reports on the morphology of the ACI graft.[1-4,14,21] However, caution is required in interpreting our results since we undertook only a small number of biopsies. Furthermore, there is evidence to suggest that cartilage grafts continue to remodel after the first post-operative year.[2] A higher frequency of hyaline-like repair would therefore be expected if biopsies were performed two to three years after implantation.

The rate of hypertrophy of the graft was low in both ACI-C (9%) and MACI groups (6%) and only two patients (2%) required an early arthroscopy because of symptomatic hypertrophy. A further six patients (7%) required manipulation under anaesthesia because of a restricted range of flexion. By comparison, Peterson et al[2] reported that 26% of 101 patients treated by ACI-P developed graft or periosteal hypertrophy with a further 10% developing intra-articular adhesions. Other authors have reported rates of re-operation for graft hypertrophy or adhesions after ACI-P of between 18%[7] and 25%.[22] The lower rate of re-operation associated with both ACI-C and MACI is a lower burden to both the patient and health resources.

The mechanical stability of fibrin glue has previously been questioned[23] although we did not observe any early delamination of the MACI graft which would suggest that fibrin glue provided inadequate fixation. The rate of failure of the graft was none in the ACI-C group and 4% in the MACI group, which compared favourably with the reported failure rate of between 5% and 11% for ACI-P.[2,21,22,24] It is unclear whether our low failure rates were due to better stability of the ACI-C and MACI grafts or to our preference for initial immobilisation of the knee in plaster.

The action of fibrin glue on transplanted chondrocytes remains controversial. After finding that chondrocytes did not migrate into fibrin glue, Brittberg et al[25] concluded that the material was not a suitable scaffold for the treatment of osteochondral defects. However, studies of the MACI membrane have shown migration of chondrocytes from the membrane into fibrin glue within two weeks of implantation.[26] Such findings have led authors to conclude that fibrin glue functions as an integral component of the MACI bioscaffold.[27] Histological examination of MACI graft biopsies in our study showed that the cartilage was well integrated into the underlying subchondral bone. While this suggests that any deleterious action of fibrin glue on migration of transplanted chondrocytes may be minor, it remains our policy to apply fibrin glue sparingly to an MACI graft.

Despite significant improvements in the functional score for both groups, the proportion of patients who achieved good to excellent clinical scores was lower than reported in other studies of the ACI-P technique. Peterson et al[2] reported a good to excellent clinical outcome in 92% of isolated lesions of the medial femoral condyle after two to nine years. Minas[22] reported that 87% of patients showed improvement after ACI-P. However, direct comparison with our results is probably inappropriate because of significant differences in the patient populations, the characteristics of the lesion and methods of assessment.

Current national guidelines in the United Kingdom recommend that ACI should be reserved for patients in whom earlier treatments for defects of the articular cartilage have failed.[28] As a consequence, most patients in our study had poor pre-operative function and a long history of symp-

toms with numerous earlier surgical procedures. These characteristics are poor prognostic indicators. It is thus essential that these factors are taken into account, as well as the properties of the chondral lesion during patient selection, counselling and outcome review.

MACI is quicker to perform than ACI, which is advantageous when combining the technique with other interventions such as ligamentous reconstruction, bone grafting, or high tibial osteotomy. Suture-free application of the MACI membrane allows implantation through a smaller surgical exposure, and is preferable when adequate fixation of the graft with sutures would be impossible because of poor containment of or access to the defect.

Our results represent an early comparison of two techniques of ACI for treatment of osteochondral defects of the knee. We have found encouraging and comparable results with both ACI-C and MACI techniques. These procedures are associated with fewer graft-related complications and re-operations compared with those reported after ACI-P. The technical and theoretical advantages of MACI have led to the operation being favoured by surgeons performing chondrocyte transplantation. Unlike ACI-P however, little is known of the long-term durability of the MACI graft. Before widespread adoption of MACI, further longer-term assessment of the procedure is needed.

One or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

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