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Instructional lecture

Autologous chondrocyte implantation: where do we stand now?

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Abstract Chondral damage to the young knee is common. In symptomatic patients current surgical treatment has focused on filling the defect with fibrocartilage; however, this tissue has poor resistance to shear forces, leading to failure and the onset of degenerative osteoarthritis.

Introduction

The success of autologous chondrocyte implantation (ACI), as an alternative treatment for symptomatic chondral defects, was first reported by Brittberg et al. in 1994.[1] The technique involved filling the defect with the patient's own cells to restore the hyaline cartilage. These cells had been harvested from the trochlear groove of the patient, grown in the laboratory, and then reimplanted underneath a periosteal membrane to contain the cells within the defect. The membrane was sutured over the defect and sealed with Tissel Fibrin glue (Baxter, Deerfield, IL, USA) to ensure that it remained watertight.[2] Brittberg et al. confirmed a hyaline-type repair, with the presence of type II collagen, on performing an arthroscopy and biopsy at 1 year.[1] Further reports have suggested that the regenerate is durable with continued improvement in patient's symptoms up to 11 years.[3,4]

This article provides a concise review of autologous chondrocyte implantation and reports the senior author's experience with this technique at the Royal National Orthopaedic Hospital, Stanmore, UK for managing symptomatic chondral knee defects.

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Structure, properties, and function of articular cartilage

Hyaline articular cartilage consists of 65%–80% water, 15%–22% collagen (wet weight), and 4%–7% aggrecan.[5] The only cells in articular cartilage are chondrocytes, and they account for less than 5% by volume.[6] The chondrocytes are responsible for the normal synthesis and degradation of extracellular matrix (ECM) components and in the adult have low metabolic activity, low matrix turnover, and only occasionally divide.[7] The chondrocytes are dispersed throughout the matrix and lie in lacunae. They are not in contact with each other but, instead, interact with the ECM. Articular cartilage does not have a blood or nerve supply, and it relies on receiving its nutrients by diffusion through the ECM.[8] It therefore has limited capacity to repair itself after injury or an inflammatory process such as rheumatoid arthritis (RA).[7]

Articular cartilage is a specialized connective tissue covering apposing joint surfaces. It is perhaps the most important tissue of a synovial joint and is well adapted to perform an exacting mechanical function. It is a nonhomogeneous, nonlinear, anisotropic, solid structure that provides stiffness, elasticity, and absorption of external compressive, tensional, and shear forces. It thus helps distribute stress evenly and prevent stress peaks within the joint.[9] These biomechanical properties are principally provided by the ECM. Articular cartilage is essentially a type II collagen sponge supported by water molecules attached to proteoglycans, which are produced by chondrocytes. The major structural polymers are type II collagen and proteoglycan aggregates composed of aggrecan, link protein, and hyaluronan. The collagen network gives the articular cartilage its tensile strength as the fibers are aligned in such a way that the compressive forces are distributed evenly.[9] The aggrecan aggregate is highly hydrophilic and lies embedded in the collagen fibrillar network.[5] Compressive

forces are resisted by a hydrostatic pressure generated by viscous drag and swelling pressure. The aggrecan aggregate is underhydrated, and the resultant swelling pressure gives healthy cartilage its ability to withstand long-term compression.[5] For shorter periods of time, less than 6 h, compressive forces are largely resisted by a hydrostatic pressure generated by the resistance of flow of fluid through the ECM.[5]

Articular cartilage is highly organized and consists of four layers, or zones: superficial layer, transitional layer, radial layer, and calcified cartilage layer.[10] In the superficial layer the cells are flattened and lie parallel to the surface. Likewise, the collagen fibrils also run parallel to the articular surface, maintaining the tensile properties of the cartilage and enabling it to resist shear forces during normal joint function and loading.[10–12] This layer has the highest water content, with more collagen and less proteoglycan than the other layers.[13,14] The transitional layer has a makeup (in both morphology and ECM composition) that lies between that of the superficial and radial zones. Here the cells are more rounded and produce more proteoglycan and less collagen (although the fibrils are thicker) than the superficial layer.[10] In the radial layer, the cells are aligned in columns perpendicular to the joint surface.[10] This layer is the largest with the thickest collagen fibers, the most concentrated proteoglycans, and the lowest water content.[10] The "tidemark" lies between the radial and calcified cartilage layer. The purpose and structure of this area is uncertain; however, as it is an undulating junction, it may help tether the cartilage by increasing the contact area between the layers.[15] The deepest layer, which is calcified cartilage, forms the transition between the soft articular cartilage and the hard underlying bone. It functions to help prevent the shearing of cartilage from bone. The cells are almost completely surrounded by calcified cartilage, suggesting that they have a low metabolic rate.[15]

In normal articular cartilage, chondrocytes rarely divide and there is a very slow ECM turnover. It has been reported that synovial fluid has a low oxygen tension (4%–10%) and that articular cartilage is even more hypoxic.[16] At the surface of articular cartilage there is an oxygen tension of about 10%, whereas in the deepest layers it is about 1%.[17] This means that chondrocyte metabolism is mainly anaerobic, with the conversion of glucose to lactic acid.[17] Articular cartilage has a low metabolic rate compared to other tissues, such as muscle; but when damaged the chondrocytes form clusters, and cellular activity increases.[10] Articular cartilage is thicker, with greater proteoglycan content, in load-bearing areas and thinner in areas where loading is minimal.[18] Mechanical loading affects the morphology and metabolic activity of the chondrocytes.

Injuries to articular cartilage

In most cases, the clinical application of cartilage repair is predominantly in patients under the age of 40 years who have lesions causing symptoms such as pain, instability, locking, and swelling. A number of painful conditions can lead to early osteoarthritis (OA), including previous ligament and meniscal injuries of the knee followed by persistent pain; osteochondral fractures after sporting injuries, which can occur in isolation or with ligament or meniscal injuries; and chondromalacia patellae, which is a common condition in adolescents resulting in the breakdown of the articular cartilage of the patella that is recognized at arthroscopy.[19] Osteochondritis dissecans (OCD) is a rare condition of teenagers and young adults. Fragments of cartilage, with or without the underlying bone, become separated from the joint surface, which can give rise to loose bodies in the joint.[20]

The true incidence of chondral injuries of the knee is unknown. Many lesions, especially those that are partial thickness, are asymptomatic; and there is no scientific evidence justifying surgical treatment for them. Twyman et al. reported on the long- term outcome of 22 knees with osteochondral lesions of the knee diagnosed before skeletal maturity.[20] They found that when followed-up prospectively into middle age 32% had symptomatic OA at 33.6 years. Shelbourne et al. reported on the long-term outcome of untreated chondral defects detected at anterior cruciate ligament (ACL) reconstruction compared to patients without chondral defects.[21] They found that there was a poorer outcome in the group with a chondral defect; but symptoms in both groups were mild. However, it is well known that full-thickness chondral defects have a poor capacity for regeneration and repair. Noyes et al. reported that 25% of knee injuries with acute haemarthrosis are associated with cartilage damage.[22] Furthermore, on a review of 31 516 arthroscopies, full-thickness loss of articular cartilage was found in 5% of patients less than 40 years; and of these cases, 63% were osteochondral injuries.[23] Prior to magnetic resonance imaging (MRI) there was a delay in diagnosis, because in one third of patients chondral injuries were not detected on routine radiography.[24]

With the advent of MRI, it is now known that "bone bruising" of the articular surface at the subclinical level is common when patients sustain an injury to the knee. Bone bruising is the result of blunt trauma to the subchondral bone and may indicate a microtrabecular fracture. Much of the research has involved the ACL-injured population. Bruising is a focal signal abnormality best appreciated on short TI-weighted inversion recovery (STIR) sequences.

Management options for symptomatic chondral defects

Various methods have been used by orthopedic surgeons to manage patients with severe and persistent pain caused by osteochondral injury, many of which aim to induce fibrocartilagenous reparative tissue (Table 1). The methods include débridement, drilling and fixation, abrasion chondroplasty, microfracture, and the insertion and use of carbon fiber pads. Other treatment strategies aim for repair with hyaline cartilage. Each treatment method has advantages and disadvantages (Table 2).

Autologous chondrocyte implantation

Chondrocyte culture

In 1986, Aston and Bentley were the first to culture rabbit chondrocytes and use them successfully to treat full-thickness articular defects.[25] In 1994, Brittberg et al. published their work on using autologous cultured chondrocytes to treat full-thickness chondral defects of the knee.[1] The cells were harvested from the medial aspect of the trochlea during an arthroscopy assessing the suitability of the patient for the technique. Cartilage specimens were minced, washed, and digested; and the resulting cells were cultured in suitable medium. The transplantation of cells took place 2–3 weeks after the initial arthroscopy and biopsy. The final volume of the cell suspension was 50–100 µl, with a total of 2.6 million to 5.0 million cells. At reimplantation the cells were injected into the defect, which had been carefully prepared and sealed with a periosteal flap sutured around the defect. Brittberg et al. were the first to report the successful treatment of isolated chondral defects of the knee, with 1-year postimplantation biopsies of the repair tissue in some of the patients showing hyaline-like cartilage.

Table 1. Fibrocartilage and hyaline cartilage repair

Fibrocartilage repair techniques
Conservative physiotherapy
Débridement
Drilling and fixation
Abrasion chondroplasty
Microfracture
Hyaline cartilage repair techniques
Articular cartilage autografting
Osteochondral allografting
Autologous chondrocyte implantation

ACI/MACI techniques

Autologous chondrocyte implantation (ACI) combined with a periosteal flap was first implanted in the human knee in 1987. This was used for the repair of knee articular cartilage defects that were symptomatic.[1,3,4] Implantation consisted of an arthrotomy, preparation of the defect, harvesting of a periosteal flap (from the proximal tibia), securing the flap to the defect, securing a watertight seal with fibrin glue, implanting the cultured chondrocytes, and then wound closure and postoperative rehabilitation.

The initial report was of 23 patients with deep cartilage defects of the knee, with an age range of 14–48 years.[1] The full-thickness cartilage defects ranged in size from 1.6 to 6.5 cm^2. The patients were followed up

Table 2. Advantages and disadvantages of the treatment methods

Treatment	Advantages	Disadvantages
Arthroscopic shaving/ débridement	Minimally invasive Cost-effective Short rehabilitation time	Recurring symptoms Progressive deterioration
Microfracture	Cost-effective Technically feasible Reported improvement in function and symptoms of 75% of patients, average 7 years after operation	Does not produce hyaline cartilage
Mosaicplasty	High survival rate of chondrocytes Hyaline cartilage characteristics	Donor site morbidity Poor matching of articular surface and fibrocartilage formation in gaps
Massive osteochondral allografts	High survival rate of chondrocytes Hyaline cartilage characteristics	Immunological reaction and disease transmission Cell viability and fixation problems Limited supply of grafts Long rehabilitation
Autologous chondrocyte implantation	Hyaline cartilage repair and characteristics Autologous cell implantation One-time treatment	Restricted activity for 1 year to allow cell integration Expensive Two surgeries

for 16–66 months (mean 39 months), and it was noted that initially the transplants reduced knee locking and pain and swelling in all patients. At 3 months, arthroscopy showed that the transplants were level with the surrounding tissue. At 2 years after transplantation, 87.5% of the patients with medial femoral condylar lesions had good or excellent results, although two patients required a second procedure because of severe central wear on the transplant with locking and pain. In terms of patellar transplantation, the results were good or excellent in 28.5% of patients, fair in 43% of patients and poor in 28.5%. It was noted that another two patients required a second procedure because of severe chondromalacia. Biopsies were performed and showed that 73% of the femoral transplants and 14% of the patellar transplants had regions of hyaline cartilage. It was therefore concluded that cultured autologous chondrocytes can be used to repair deep cartilage defects in the femoral and tibial articular surfaces of the knee joint.

Peterson et al. have reported on 61 cases that have now been followed up for a mean of 7.4 years (range 5–11 years).[4] The results after 2 years confirmed that 82% of patients had good or excellent outcomes, and at 5–11 years 84% of patients again were good or excellent. A few patients underwent arthroscopy at a mean of 54 months; it showed that 73% demonstrated more than 90% stiffness of the reparative tissue using electromechanical indentation probes; and on biopsy 67% were hyaline-like. They concluded that ACI had a durable outcome for as long as 11 years. Peterson et al. also reported that among 58 patients with osteochondral defects of the knee (39 of which were of the medial condyle and 19 of the lateral femoral condyle) 91% had good or excellent outcomes after a follow-up of 2–10 years.[26] Other surgeons have since produced similar encouraging early results with osteochondral defects in the femoral condyle using the same technique.[27–30]

This technique of harvesting periosteum to use as a flap, usually taken from the proximal tibia or distal femur, can be difficult especially in patients over 35 years of age. Furthermore, suturing the harvested flap into the edges of the defect can potentially damage the surrounding healthy articular cartilage. Also, the role of the periosteum in the production of hyaline-like articular cartilage is controversial. Some think that it is important, especially the cambium layer, whereas others believe that if the cultured chondrocytes are of good quality the periosteum may have no role to play other than as a seal to keep the cells within the defect.[31] A recent article reported 497 adverse events among a group of 294 patients undergoing ACI using the periosteum patch technique.[32] The most common complication was graft failure, accounting for 25%. Tissue hypertrophy, also reported by Peterson et al.,[3] was seen in 22% of cases and may be a problem with specific use of the periosteum.[32]

In view of this, the importance of the periosteum patch in ACI and the regenerative tissue has been raised; and since 1998 surgeons at the Royal National Orthopaedic Hospital Trust have attempted to answer this question by using an inert type I/III collagen membrane to cover the defects and rely on the cultured chondrocytes alone to form the regenerative tissue.

The two-stage operative technique involves the following.

First Stage

1. Arthroscopic chondrocyte harvest from a non-load-bearing region of articular cartilage (e.g., medial edge of the trochlear groove)
2. Chondrocyte culture (approximately 6 weeks) ± incorporation on a tissue scaffold — depending on whether patient randomised to ACI-C (ACI underneath the collagen membrane) or MACI (matrix-induced ACI)

Second Stage

1. Arthrotomy and preparation of defect by débriding edges to normal articular cartilage
2. Implantation of chondrocytes

Cultured chondrocytes can be reimplanted underneath the collagen membrane (ACI-C) (Fig. 1). Alternatively, during matrix-induced autologous chondrocyte implantation (MACI) the cells are cultured in the same manner as ACI-C but are then seeded directly onto the membrane's rough surface; the membrane acts as a carrier for the cells. The membrane is then inserted directly into the defect, with the cells lying against the intact subchondral plate (Fig. 2). The inert collagen membrane is resorbed within a few months, leaving the cells and the regenerative tissue.

A personal 7-year experience with autologous chondrocyte implantation

Patients and methods

This prospective cohort study of ACI, with the addition of MACI since 2003, was conducted at a single center by the senior author. Prior ethics approval was obtained.

Since 1998, all patients undergoing ACI or MACI by one surgeon (TWRB) were entered into this prospective study. In total, 156 patients (88 male, 68 female) with a mean age of 33.4 years (range 15–52 years) were operated on, with the primary indication for surgery being persistent pain resulting from an isolated osteochondral defect > 1 cm^2 in the articular surface of the knee. Trauma, osteochondritis dissecans, and chondro-

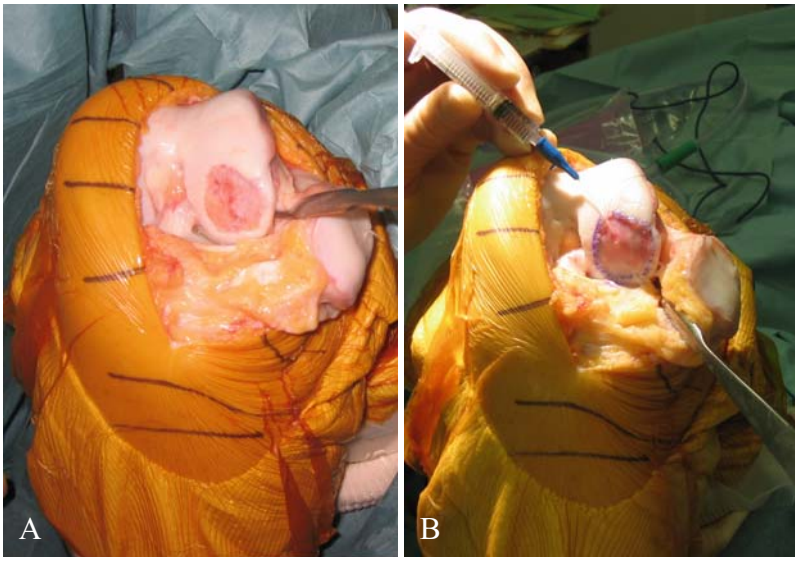

Fig. 1. Autologous chondrocyte implantation (ACI) procedure. **A** Chondral defect following débridement. **B** Water test being performed prior to insertion of the cultured chondrocytes

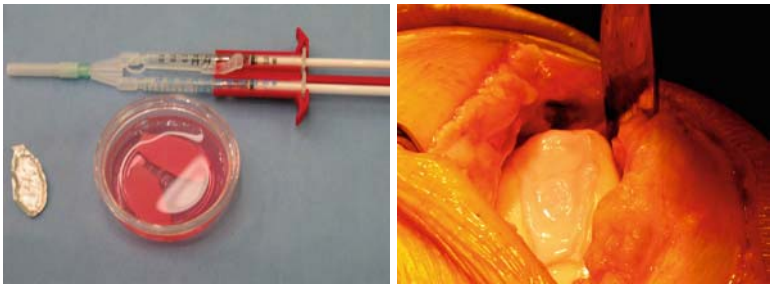

Fig. 2. Matrix-induced ACI (MACI) membrane that has been secured into the defect with Tissel glue around the perimeter

malacia patellae were the principal indications for surgery, with a large proportion of patients having previously undergone other surgical treatments.

All patients entered a structured rehabilitation program. Joint instability, abnormal joint alignment, osteoarthritis, and inflammatory joint disease were all exclusion criteria. Since 2003, patients have been randomized to ACI or MACI as part of an ongoing multicenter clinical study.

In addition to the normal preoperative investigations, all patients were assessed prior to chondrocyte implantation using the following validated clinical scoring systems.

- Modified Cincinnati Rating Score (MCRS)[33] (0–100)
- Visual Analogue Score (0–10)
- Bentley Functional Rating Score (BFRS)[34] (0–4)
- Lysholm and Gilchrist Score (LG)[35] (0–100)
- Patient Functional Outcome Score (PFOS) (0–10)
- Brittberg Score (poor, fair, good, excellent)[1]
- Patient Rating Score (PRS) (better, same, worse)

Annual functional outcome was assessed using a postal questionnaire with the same scoring systems. The response rate was above 85% throughout all annual patient assessments. Patients lost to follow-up were allocated poor/low outcome scores.

The size of the osteochondral defect was similar in both the ACI and MACI groups, with three patients having dual defects treated with ACI and nine patients having dual defects treated with MACI. The area of the osteochondral defects repaired using ACI (3.14 cm^2, range 1.0–7.0 cm^2) was not significantly different ($P < 0.07$) from those treated using MACI (4.35 cm^2, range 1.0–12.2 cm^2).

Results — clinical outcome

The sequential MCRS for ACI and MACI are detailed in (Fig. 3) and Table 3, with the corresponding statistical significance in comparison to the preoperative level using an unpaired *t*-test.

Although at 1 year ACI demonstrated a significantly better MCRS than did MACI (unpaired *t*-test, $P = 0.021$), there was no significant difference ($P > 0.05$) between the two techniques in subsequent years.

Compared to the preoperative VAS, both ACI and MACI show sequential significant improvement on the postoperative VAS ($P < 0.0001$, unpaired *t*-test)

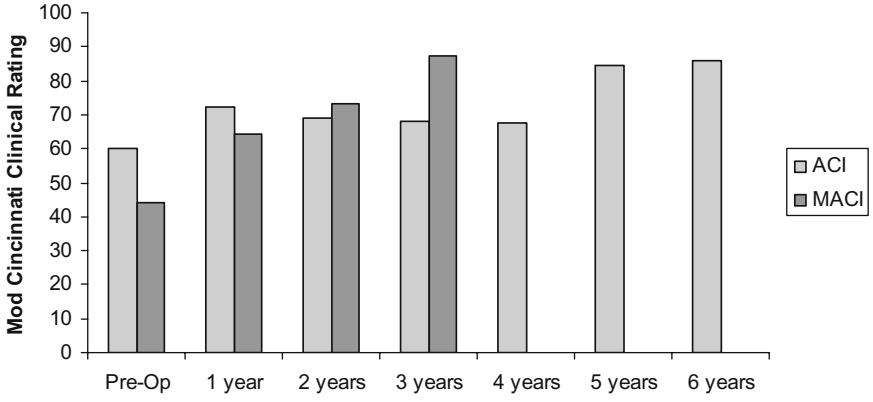

Fig. 3. Sequential modified Cincinnati Rating Score for ACI and MACI. Both techniques demonstrated sequential, significant improvement ($P < 0.0001$)

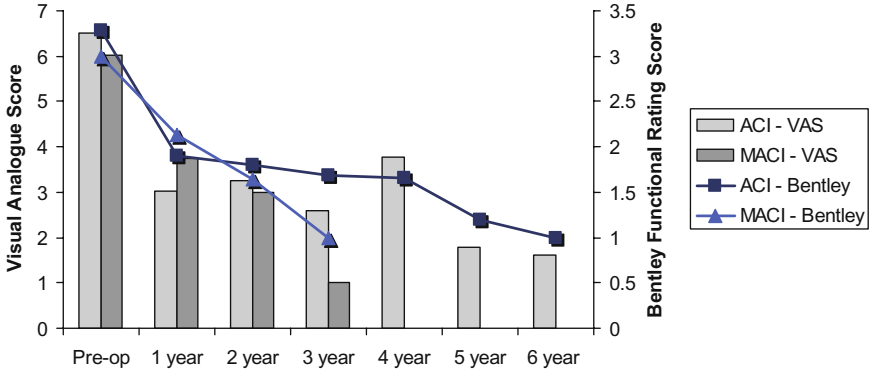

Fig. 4. Sequential Bentley (*Bentley*) Functional Rating and Visual Analogue (*VAS*) scores for ACI and MACI. Both techniques demonstrated sequential, significant improvement ($P < 0.0001$)

Table 3. Sequential modified Cincinnati Rating Score for ACI and MACI

	ACI		MACI	
Time of score	Score	*P* relative to preop. value	Score	*P* relative to preop. value
Preop.	60.13		44.03	
1 Year	72.07	<0.0001	64.23	<0.0001
2 Years	69.07	<0.0001	73.45	<0.0001
3 Years	67.96	<0.0001	87.33	<0.0001
4 Years	67.48	<0.0001		
5 Years	84.60	<0.0001		
6 Years	85.80	<0.0001		

ACI, autologous chondrocyte implantation; MACI, matrix-induced ACI; preop., preoperatively

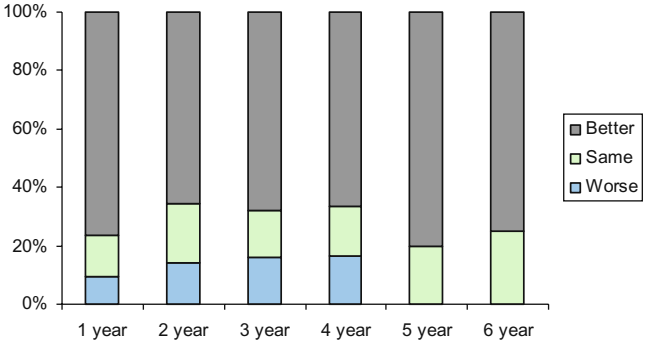

Fig. 5. Sequential combined ACI and MACI patient rating scores. Both techniques demonstrated postoperatively a significant increase ($P < 0.0001$) in the percentage of patients describing their knee function as "better"

(Fig. 4). There was no significant difference ($P > 0.05$) in the VAS between ACI and MACI up to 2 years of follow-up.

There was no significant difference ($P > 0.05$) in the BFRS between ACI and MACI up to 2 years after surgery, although both techniques demonstrated significant and sequential improvements ($P < 0.0001$, unpaired *t*-test) in comparison to their preoperative scores (Fig. 4).

The overall combined 6-year PRS results for both techniques are shown in Fig. 5, which indicates that most of the patients (>60%) described their knee function as "better."

All PFOS scores were significant (unpaired *t*-test, $P < 0.0001$) in comparison to the respective mean preoperative scores (Table 4). Comparing the two techniques, ACI had superior PFOS scores at 1 year in comparison to MACI ($P = 0.0454$), although there was no significant difference ($P > 0.05$) in subsequent years. Similar to the PFOS, there are sequential annual improvements in the LG scores for both ACI and MACI, with ACI being

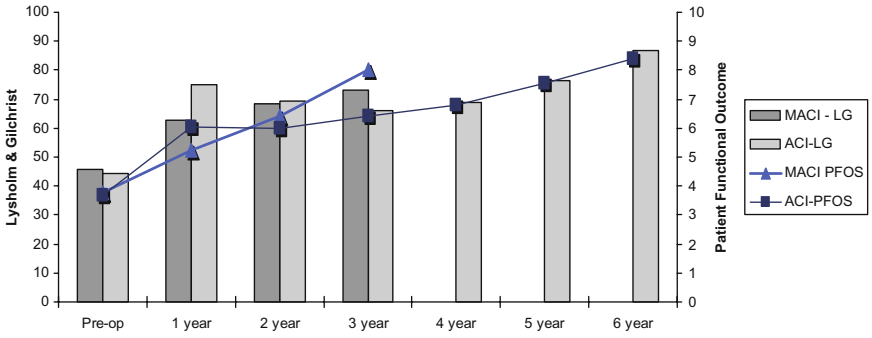

Fig. 6. Sequential improvement in the Patient Functional Outcome Score (*PFOS*) and Lysholm and Gilchrist score (*LG*) following ACI and MACI. Both techniques demonstrated sequential, significant improvement ($P < 0.0001$)

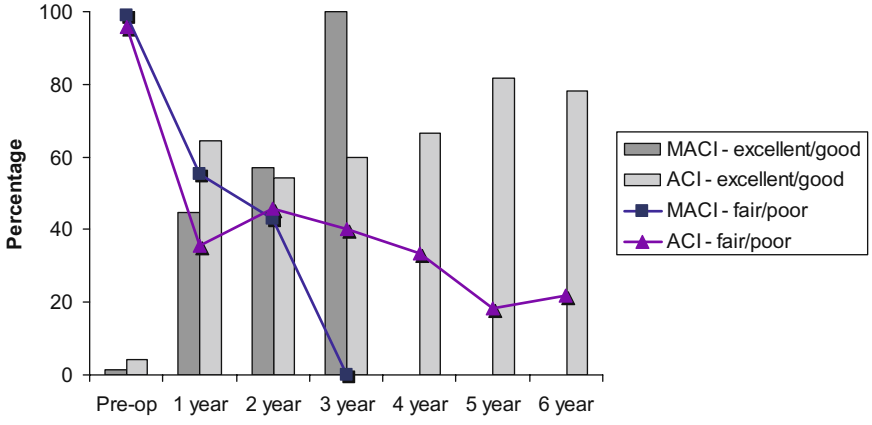

Fig. 7. Sequential ACI and MACI improvements in Brittberg scoring (excellent/good vs. fair/poor). Both techniques demonstrated a sequential, significant increase in beneficial responses, with a corresponding reduction in adverse responses ($P < 0.0001$)

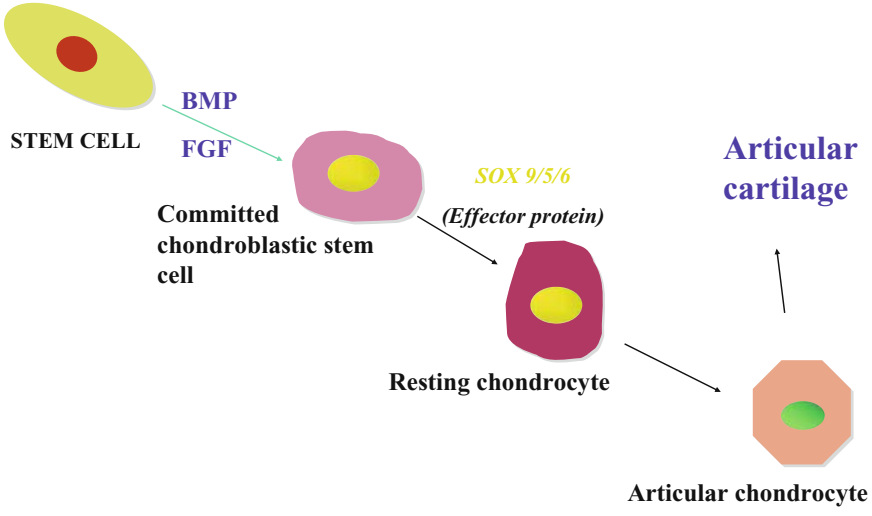

Fig. 8. Pathway involved in BMP stimulation of mesenchymal stem cell differentiation into articular chondrocytes. *BMP*, bone morphogenetic protein; *FGF*, fibroblast growth factor

Table 4. Sequential improvement in Patient Functional Outcome Score following ACI and MACI

Time of score	ACI	MACI	*P* for ACI /MACI
Preop.	3.68	3.78	
1 Year	6.05	5.23	0.0454
2 Years	5.97	6.43	0.4261
3 Years	6.43	8.00	>> 0.05
4 Years	6.79		
5 Years	7.54		
6 Years	8.40		

significantly better at 1 year ($P = 0.0066$), but no significant difference ($P = 0.89$) between the techniques at 2 or 3 years (Fig. 6).

The rate of improvement seen with both techniques was quantified using the trendline gradient. Trendlines created from both LG and PFOS scores exhibit a coefficient of determination of >0.87. These data identified MACI as having a rate of annual improvement superior to that of ACI.

Table 5. Correlation between timing of biopsy and histology result

Histological diagnosis	Biopsy at <2 years ($n = 92$)	Biopsy at >2 years ($n = 23$)
Hyaline-like	18 (19%)	11 (48%)
Mixed hyaline + fibrocartilage	19 (21%)	6 (26%)
Fibrocartilage	53 (58%)	6 (26%)
Fibrous tissue	2 (2%)	0

The Brittberg rating enabled patients to score their knee function subjectively as poor, fair, good, or excellent. Figure 7 shows the sequential results for both ACI and MACI techniques, with responses being grouped as "excellent or good" compared with "fair or poor." Continued sequential increases in beneficial responses (good or excellent) from the preoperative level were observed for both techniques (bars in Fig. 7), with a corresponding reduction in adverse responses (lines in Fig. 7). The rate of improvement of beneficial responses and the rate of decline of adverse responses — using the trendline gradient — was three times greater for MACI than for ACI.

Results — histology

The mean timing of the biopsy was 14.8 months (range 3–55 months). The biopsy results show that in group A (biopsy performed < 2 years; $n = 92$) 19% had hyaline-like cartilage, 58% fibrocartilage, 21% mixed tissue, and 2% fibrous tissue. Group B (biopsy performed > 2 years; $n = 23$) had 48% hyaline-like cartilage, 26% fibrocartilage, and 26% mixed tissue (Table 5). A moderate correlation (φ and Cramer's V 0.297, $P = 0.017$) was found between the type of tissue and the timing of the biopsy.

Discussion

Outcome studies over the past decade have helped refine the indications and techniques for ACI, demonstrating continued improvement in clinical results.

The strength of this study is based on the utilization of seven independent scoring systems to evaluate the functional outcomes following autologous chondrocyte implantation using either the ACI or MACI technique for up to 6 years of follow-up. The MCRS, PFOS, and LG score indicated continued improvement in the patients' knee function. Significant improvement was reported in all scores compared to preoperative scores ($P < 0.0001$). The VAS, BFRS, and PFOS indicated there was significant improvement compared to the preoperative scores ($P < 0.0001$), and the scores indicated annually that the improvement had been maintained up to 6 years.

The technical ease and practical advantages of MACI have led to its preference by some surgeons performing chondrocyte transplantation, although the long-term durability and survivorship of the MACI graft is currently unknown. Furthermore, although our results suggest that MACI has a superior rate of clinical improvement in comparison to ACI, further clinical and histological evidence are required to validate either technique.

Our histology results suggest that repair tissue remodels and its quality improves with time: In later biopsies, hyaline tissue had more than doubled, fibrocartilage had halved, and fibrous tissue was no longer found. The results from this study are encouraging and provide further evidence of the benefit in the medium term of transplanting autologous chondrocytes to areas of osteochondral defects.

Conclusion

Compared with presurgical scores, the postoperative scores show statistically significant improvement during follow-up. The improvement has been maintained for up to 6 years of follow-up.

Future of autologous chondrocyte implantation

At present, medium-term results of ACI, using either periosteum (ACI-P) or manufactured collagen (ACI-C) membrane look encouraging, but long-term results are awaited. However, the fundamental question of the importance of the cultured chondrocytes in the reparative process needs to be answered. Hence, a prospective randomized blinded study is under way at our institution that will compare matrix-assisted chondrocyte implantation (MACI), which we have shown to be as effective as ACI-C at 3 years, against microfracture covered with the type I/III collagen membrane (autologous matrix-induced chondrogenesis, or AMIC). This will allow direct comparison between marrow stimulation techniques and cultured chondrocytes. Research is

also underway in second-generation engineering techniques, such as arthroscopic implantation of cells, and delivering the chondrocytes on a three-dimensional matrix/gel.

There is also evidence that the reparative process can be influenced and enhanced by bone morphogenetic proteins (BMPs), which are members of the transforming growth factor-β superfamily.[36] They are multifunctional growth factors and stimulate cells to proliferate.[37] They also have two other functions: BMP signalling is required for the formation of precartilaginous condensations from the mesenchymal precursors and for the differentiation of precursors into chondrocytes.[37]

It is known that BMP-2, -4, -6, -7, -9, and -13 stimulate the synthesis of type II collagen and aggrecan by adult chondrocytes, which are the main constituents of the cartilage matrix.[36] Researchers have also shown that the local delivery of BMPs by genetically engineered stem cells enhances chondrogenesis and repair of articular cartilage.[38] To date, this has been shown only in animal experiments; no human studies have been undertaken. This is because enhanced BMP activity has been reported in some tumor cells, such as breast carcinoma, and one should question whether enhancement with BMPs may have the potential for tumorigenesis.[39]

Bone morphogenetic proteins also stimulate the chondrogenic differentiation of stem cells, another important avenue of research in cartilage repair. It has been shown that BMP-4 and other BMPs can induce embryonic stem cells and mesenchymal progenitor cells to undergo chondrogenesis[36,40] (Fig. 8). The mesenchymal differentiated chondrocytes induce cartilage repair similar to ACI within 4 weeks after transplantation in vivo.[41] This does not require the use of collagen scaffolds (unlike MACI) and is currently under investigation.

Conclusions

Untreated, articular cartilage defects of the knee may cause pain and/or disability and may ultimately progress to early OA. The aim of any cartilage repair technique is to produce a joint that moves fully without pain and a repair that is durable for the medium/long-term. It is hoped that if a durable repair can be achieved this in itself may prevent further deterioration of the local cartilage and the subsequent development of osteoarthritis.

Autologous chondrocyte implantation has become a popular technique for treating isolated chondral defects of the knee and has now been performed on an estimated 10000 patients worldwide. Most groups have reported good to excellent clinical and histological results following this technique.[26,31,42–45] However, there is still scepticism among many surgeons on its effectiveness, the type of repair produced, and its durability. Surgeons are still uncertain on whom it should be used and the timing of its use in relation to other techniques, such as microfracture.

Based on a review of the available literature and our study looking at the clinical outcomes for isolated chondral defects of the knee using autologous chondrocyte transplantation, we are able to draw a number of conclusions.

- There is no current evidence to justify treatment of asymptomatic chondral defects of the knee.
- Adult patients with symptomatic full-thickness defects do poorly if not treated.
- Young patients have better outcomes.
- Patients who undergo ACI earlier do better.
- Always correct instability/malalignment.
- Small, well-contained lesions may be suitable for microfracture.
- In patients who fail microfracture, ACI offers a satisfactory alternative salvage procedure.
- ACI-C leads to significant improvement in objective and patient-reported clinical outcome scores (74%).
- ACI-C produces durable outcomes for as long as 7 years.
- Clinical results of ACI-C and MACI techniques are comparable at 3 years.
- The percentage of hyaline cartilage at biopsy appears to improve with time.

Further research is crucial to enhance our understanding of the molecular and cellular events involved in cartilage repair. With this information we can improve the outcome for patients.

References

1. 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.
2. Brittberg M, Sjogren-Jansson E, Lindahl A, Peterson L. Influence of fibrin sealant (Tissele) on osteochondral defect repair in the rabbit knee. Biomaterials 1997;18:235–42.
3. 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.
4. 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.
5. Comper WD. Physicochemical aspects of cartilage extracellular matrix. In: Hall B, Newman S, editors. Cartilage: molecular aspects. Boca Raton, FL: CRC Press; 1991. p. 59–78.
6. Poole AR, Rosenberg LC, Reiner A, Ionescu M, Bogoch E, Roughley PJ. Contents and distributions of the proteoglycans decorin and biglycan in normal and osteoarthritic human articular cartilage. J Orthop Res 1996;14:681–9.

7. Muir H. The chondrocyte, architect of cartilage: biomechanics, structure, function and molecular biology of cartilage matrix macromolecules. Bioessays 1995;17:1039–48.
8. Tortora GJ, Grabowski SR. Skeletal system and joints. In: Principles of anatomy and physiology. New York: Harper-Collins; 1994.
9. Mow VC, Setton LA, Guilak F, Ratcliffe A. Mechanical factors in articular cartilage and their role in osteoarthritis. In: Kuettner KE, Goldberg VM, editors. Osteoarthritic disorders. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995. p. 147–71.
10. Buckwalter JA, Hunziker EB, Rosenberg LC, Coutts RD, Adams M, Eyre DR. Articular cartilage: composition and structure. In: Woo SL, Buckwalter JA, editors. Injury and repair of the musculoskeletal soft tissues. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1987. p. 405–26.
11. Lane JM, Weiss C. Review of articular cartilage collagen research. Arthritis Rheum 1975;18:553–62.
12. Weiss C, Rosenberg L, Helfet AJ. An ultrastructural study of normal young adult human articular cartilage. J Bone Joint Surg Am 1968;50:663–74.
13. Wong M, Wuethrich P, Eggli P, Hunziker E. Zone-specific cell biosynthetic activity in mature bovine articular cartilage: a new method using confocal microscopic stereology and quantitative autoradiography. J Orthop Res 1996;14:424–32.
14. Kuettner KE, Aydelotte MB, Thonar EJ. Articular cartilage matrix and structure: a minireview. J Rheumatol 1991;27:46–8.
15. Oegema TR Jr, Carpenter RJ, Hofmeister F, Thompson RC Jr. The interaction of the zone of calcified cartilage and subchondral bone in osteoarthritis. Microsc Res Tech 1997;37:324–32.
16. Ferrell WR, Najafipour H. Changes in synovial PO_2 and blood flow in the rabbit knee joint due to stimulation of the posterior articular nerve. J Physiol 1992;449:607–17.
17. Lee RB, Urban JP. Functional replacement of oxygen by other oxidants in articular cartilage. Arthritis Rheum 2002;46:3190–200.
18. Rogers BA, Murphy CL, Cannon SR, Briggs TW. Topographical variation in glycosaminoglycan content in human articular cartilage. J Bone Joint Surg Br 2006;88:1670–4.
19. Maffulli N, Binfield PM, King JB, Good CJ. Acute haemarthrosis of the knee in athletes: a prospective study of 106 cases. J Bone Joint Surg Br 1993;75:945–9.
20. Twyman RS, Desai K, Aichroth PM. Osteochondritis dissecans of the knee: a long-term study. J Bone Joint Surg Br 1991;73:461–4.
21. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. J Bone Joint Surg Am 2003;85:8–16.
22. Noyes FR, Bassett RW, Grood ES, Butler DL. Arthroscopy in acute traumatic hemarthrosis of the knee: incidence of anterior cruciate tears and other injuries. J Bone Joint Surg Am 1980;62:687–95, 757.
23. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 1997;13:456–60.
24. Matthewson MH, Dandy DJ. Osteochondral fractures of the lateral femoral condyle: a result of indirect violence to the knee. J Bone Joint Surg Br 1978;60:199–202.
25. Aston JE, Bentley G. Repair of articular surfaces by allografts of articular and growth-plate cartilage. J Bone Joint Surg Br 1986;68:29–35.
26. 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;85:17–24.
27. Badolato R, Oppenheim JJ. Role of cytokines, acute-phase proteins, and chemokines in the progression of rheumatoid arthritis. Semin Arthritis Rheum 1996;26:526–38.
28. Gillogly SD, Voight M, Blackburn T. Treatment of articular cartilage defects of the knee with autologous chondrocyte implantation. J Orthop Sports Phys Ther 1998;28:241–51.
29. Hubbard MJ. Articular debridement versus washout for degeneration of the medial femoral condyle: a five-year study. J Bone Joint Surg Br 1996;78:217–9.
30. Minas T. The role of cartilage repair techniques, including chondrocyte transplantation, in focal chondral knee damage. Instr Course Lect 1999;48:629–43.
31. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, 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.
32. Wood JJ, Malek MA, Frassica FJ, Polder JA, Mohan AK, Bloom ET, et al. Autologous cultured chondrocytes: adverse events reported to the United States Food and Drug Administration. J Bone Joint Surg Am 2006;88:503–7.
33. Noyes FR, Mooar LA, Barber SD. The assessment of work-related activities and limitations in knee disorders. Am J Sports Med 1991;19:178–88.
34. Meister K, Cobb A, Bentley G. Treatment of painful articular cartilage defects of the patella by carbon-fiber implants. J Bone Joint Surg Br 1998;80:965–70.
35. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med 1982;10:150–4.
36. Yoon DM, Fisher JP. Chondrocyte signaling and artificial matrices for articular cartilage engineering. Adv Exp Med Biol 2006;585:67–86.
37. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular biology of the cell. 4th edn. New York: Garland; 2002.
38. Kuroda R, Usas A, Kubo S, Corsi K, Peng H, Rose T, et al. Cartilage repair using bone morphogenetic protein 4 and muscle-derived stem cells. Arthritis Rheum 2006;54:433–42.
39. Clement JH, Raida M, Sanger J, Bicknell R, Liu J, Naumann A, et al. Bone morphogenetic protein 2 (BMP-2) induces in vitro invasion and in vivo hormone independent growth of breast carcinoma cells. Int J Oncol 2005;27:401–7.
40. Kramer J, Hegert C, Guan K, Wobus AM, Muller PK, Rohwedel J. Embryonic stem cell-derived chondrogenic differentiation in vitro: activation by BMP-2 and BMP-4. Mech Dev 2000;92:193–205.
41. Tatebe M, Nakamura R, Kagami H, Okada K, Ueda M. Differentiation of transplanted mesenchymal stem cells in a large osteochondral defect in rabbit. Cytotherapy 2005;7:520–30.
42. Briggs TW, Mahroof S, David LA, Flannelly J, Pringle J, Bayliss M. Histological evaluation of chondral defects after autologous chondrocyte implantation of the knee. J Bone Joint Surg Br 2003;85:1077–83.
43. Haddo O, Mahroof S, Higgs D, David L, Pringle J, Bayliss M, et al. The use of chondrogide membrane in autologous chondrocyte implantation. Knee 2004;11:51–5.
44. Micheli LJ, Browne JE, Erggelet C, Fu F, Mandelbaum B, Moseley JB et al. Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up. Clin J Sport Med 2001;11:223–8.
45. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. Clin Orthop 2001;391:349–61.