ASPECTS OF CURRENT MANAGEMENT

An overview of autologous chondrocyte implantation

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Chondral damage to the knee is common and, if left untreated, can proceed to degenerative osteoarthritis. In symptomatic patients established methods of management rely on the formation of fibrocartilage which has poor resistance to shear forces. The formation of hyaline or hyaline-like cartilage may be induced by implanting autologous, cultured chondrocytes into the chondral or osteochondral defect.

Autologous chondrocyte implantation may be used for full-thickness chondral or osteochondral injuries which are painful and debilitating with the aim of replacing damaged cartilage with hyaline or hyaline-like cartilage, leading to improved function. The intermediate and long-term functional and clinical results are promising.

We provide a review of autologous chondrocyte implantation and describe our experience with the technique at our institution with a mean follow-up of 32 months (1 to 9 years).

The procedure is shown to offer statistically significant improvement with advantages over other methods of management of chondral defects.

Injuries to joint surfaces can result from acute high-impact or repetitive shear and torsional loads on the superficial zone of the articular cartilage. In a retrospective review of more than 31,000 arthroscopic procedures, Curl et al. found a prevalence of 63% of chondral lesions with a mean of 2.7 lesions per knee. A prospective study of 1000 consecutive arthroscopies showed chondral or osteochondral lesions of any type in 61% of the patients, whereas focal chondral or osteochondral defects were found in 19%. In other studies the prevalence of articular lesions has been reported to range from 22% to 50%.

Articular cartilage is an avascular, aneural tissue with limited potential for repair. Chondrocytes have limited migratory ability because of their surrounding collagen matrix and therefore the normal cells around a chondral lesion are unable to fill the gap. Chondrocytes have a poor response to injury characterised by a transient, limited increase in their mitotic activity. This, together with the small number of chondrocytes normally found in articular cartilage, decreases the healing potential of chondral lesions significantly. Continuous use of the limb by the individual producing repetitive forces through any lesion, adds to an already poor environment for spontaneous repair.

When the injury involves the subchondral bone, multipotential mesenchymal stem cells are released from the bone marrow, filling the defect and leading eventually to the production of fibrocartilage. This has inferior biomechanical properties to those of articular cartilage and does not provide adequate protection of the underlying subchondral bone which, consequently is exposed to repetitive axial and shear forces leading to progressive pain and disability, especially in the high-demand patient.

Various methods have been used by orthopaedic surgeons to manage patients with severe and persistent pain caused by osteochondral injuries including debridement, drilling and fixation, abrasion chondroplasty, microfracture and the use of carbon fibre pads, all of which aim to induce fibrocartilaginous repair tissue. Other methods, including articular cartilage autografting and the use of osteochondral allografts, aim for repair with hyaline cartilage. In 1971 Bentley and Greer first showed that isolated chondrocytes could be transplanted into the tibial surface of rabbits with normal joints or with experimental arthritis and in 1994, Brittberg et.al described the use of autologous cultured chondrocytes in the treatment of full-thickness chondral defects of the knee. Cells harvested during arthroscopy were cultured in suitable media to produce autologous chondrocyte implantation...
2.6 to 5 million cells. At implantation the cells were injected into the prepared defect and sealed with a periosteal flap sutured around it. They achieved successful treatment of isolated chondral defects of the knee, with biopsies of the repair tissue taken one year after implantation showing hyaline-like cartilage in some patients. Since the introduction of this technique, other methods have been developed in an attempt to improve on these results. In second-generation techniques, including matrix-induced autologous chondrocyte implantation (MACI), the cells are cultured in the same manner, but are then seeded directly onto a type-I/III collagen scaffold which acts as a carrier for the cells, ensuring the even distribution of chondrocytes. ‘Bioseed’ (Biotissue, Freiburg, Germany) uses a gel-like polymer matrix scaffold which is initially mechanically stable but eventually, bioresorbable. Hyalograft (Fidia Advanced Biomaterials, Abano Terme, Italy) includes hyaluronic acid within the tissue scaffold. This is a glycosaminoglycan found in the extracellular matrix of articular cartilage and in mesenchymal cells in which it functions as a structural component as well as an information molecule.

We now review the clinical and histological results of autologous chondrocyte implantation (ACI) from the Royal National Orthopaedic Hospital, Stanmore, United Kingdom at a mean follow up of 32 months (1 to 9 years).

**Indications**

ACI is recommended for symptomatic International Cartilage Repair Society (ICRS) grade-III and grade-IV lesions of the femoral condyles, trochlea or patellar. Motivated, compliant patients between the ages of 15 and 55 years are the best candidates for this technique. Mosaicplasty or microfracture can be an acceptable treatment option for smaller defects (< 2 cm²). An ACI should be considered for symptomatic patients with a lesion of between 1 cm² and 12 cm² and for those whose previous treatment, such as microfracture and mosaicplasty, has failed. Associated loss of bone with a chondral defect may need staged or simultaneous bone grafting. Reciprocal or ‘kissing’ lesions are considered to be a contraindication to ACI. Although ACI in patellofemoral lesions has been found to be less successful than in other locations, recent studies have yielded better outcomes. Nevertheless, the results vary depending on the site of the lesion on the patella. Other centres have combined ACI for patellar lesions with patellar realignment to treat instability.

**Pre-operative assessment**

The physiological age, weight, pre-operative activity level and likely post-operative compliance with physiotherapy regimes must be recorded.

Clinical examination should assess the alignment of the knee and associated injuries. If abnormal alignment is suspected full-leg standing radiographs should be obtained to determine the mechanical axis through the knee and thus predict excessive loading and forces through the potential transplant site. If necessary, malalignment should be corrected by concomitant osteotomy to unload the involved compartment. Insufficiency of the cruciate ligaments should be evaluated by MRI and clinically relevant dysfunction treated by simultaneous reconstruction. Meniscal lesions need also to be addressed either by repair or by resection at the time of the first-stage arthroscopy.

Although arthroscopic assessment of chondral defects remains the optimum means of evaluation, MRI is increasingly becoming a reliable non-invasive method for diagnosing chondral and osteochondral injuries in the knee, with reported sensitivities of up to 99%. This, potentially, provides sufficient information for pre-operative planning and reduces the need for arthroscopy before the first-stage procedure. MRI also allows for simultaneous assessment of the soft tissues.

Operative technique. The first stage of the two-stage operative technique involves the arthroscopic harvest of chondrocytes from a non-load-bearing region of articular cartilage such as the medial edge of the trochlear groove followed by chondrocyte culture for approximately four to six weeks with incorporation of a tissue scaffold depending on whether collagen-covered ACI-(C) or MACI is chosen.

The second stage requires arthrotomy and the preparation of the defect by deburring the edges to normal articular cartilage. Breaking through the subchondral bone plate should be avoided to prevent bleeding into the defect. Considerable bone defects (> 6 mm deep) necessitate simultaneous bone grafting or the use of the ‘sandwich technique’. The final process is the implantation of chondrocytes (ACI with either a periosteal graft or a collagen membrane or MACI cells incorporated into a type-I/III collagen scaffold).

ACI combined with a periosteal flap was first used in the human knee in 1994, for the repair of symptomatic defects of articular cartilage. After arthrotomy and preparation of the defect, a periosteal flap was harvested from the proximal tibia. This was secured to the defect and made watertight by a fibrin-glue seal before the insertion of the cultured chondrocytes.

Cultured chondrocytes can be re-implanted beneath a collagen membrane (ACI-C) (Fig. 1). With the MACI technique the cells are cultured in the same manner as for ACI-C, but are then seeded directly on to a collagen type-I/III scaffold which acts as a carrier for the cells and ensures the even distribution of chondrocytes (1 million cells/cm²). The membrane is then inserted directly into the defect with the cells lying against the intact subchondral plate. The inert collagen membrane is resorbable in a few months leaving the cells and the regenerative tissue.

The technique of harvesting periosteum for use as a flap, usually taken from the proximal tibia or the distal femur, can be difficult especially in patients over the age of 35 years. Suturing of the harvested flap into the edges of the defect can potentially damage the surrounding healthy articular cartilage. The role of the periosteum in the production of hyaline-like articular cartilage is controvers
sial. Some think that it is important, especially the cambium layer, while others believe that if the cultured chondrocytes are of good quality the periosteum may have no role to play other than to act as a seal to keep the cells within the defect.\textsuperscript{24,25} A recent study reported a total of 497 adverse events in a group of 294 patients undergoing ACI using the periosteum patch technique.\textsuperscript{26} Of these, the most common complication was failure of the graft which occurred in 25\%. Tissue hypertrophy, also described by Peterson et al,\textsuperscript{16} was seen in 22\% of cases and may be a problem related specifically to the use of periosteum.\textsuperscript{26} Since 1998 surgeons at the Royal National Orthopaedic Hospital have attempted to address this by using an inert type-I/III collagen membrane to cover the defects, relying on the cultured chondrocytes alone to form the regenerative tissue.

**Post-operative rehabilitation**

Maturation of the cartilage occurs through several phases after implantation.\textsuperscript{1} The first, termed the proliferative phase, is when the implanted cells adhere to the subchondral bone. This is followed by the transition phase in which there is expansion of the matrix released by the chondrocytes and, finally, the matrix remodelling phase when the cartilage tissue progressively acquires properties similar to those of the adjacent normal cartilage. These phases should be considered during post-operative rehabilitation and physiotherapy. Different centres have slightly different rehabilitation regimes after ACI.

The protocol implemented at the Royal National Orthopaedic Hospital is designed to avoid impact loading and twisting or shearing forces, which may damage the repair and disperse the implanted cartilage cells. After the second-stage operation the patient is managed in a cylinder of plaster-of-Paris for one week. During the first six weeks toe-touch weight-bearing only is allowed with progressive flexion-extension exercises to provide a chondrogenic stimulus, aiming at a full range of movement by six weeks. From six to ten weeks the patient is allowed to bear weight partially and from ten weeks onwards full weight-bearing can take place.

Other regimes advocate the use of continuous passive movement as early as six hours following the implantation procedure. Early mobilisation may aid the differentiation of mesenchymal cells.\textsuperscript{27,28} This is followed by a period of partial weight-bearing, varying between six and 12 weeks. The protocol for the autologous chondrocyte transplantation/implantation \textit{versus} existing treatment trial (active), currently ongoing, suggests that patients should be capable of low-impact exercise, such as cycling, by 12 weeks.\textsuperscript{28}

**Post-operative evaluation**

Arthroscopic assessment remains the optimum method of post-operative evaluation and, in some centres, including the Royal National Orthopaedic Hospital, is carried out routinely (at one year post-implantation) during follow-up. The repair is visualised directly, stiffness is assessed by probing and a biopsy can be taken to allow histological evaluation of the repair tissue.

MRI has become an increasingly important, non-invasive means of assessing articular cartilage and its repair.\textsuperscript{26,29} Advances in MRI techniques, including the use of delayed gadolinium-enhanced scans, may prove to be useful in assessment of the graft matrix and in predicting the histological phenotype.\textsuperscript{30}
Outcome of ACI
Overall, the results of ACI have been encouraging. In 1994, Brittberg et al. described the outcome after 36 months following transplantation in femoral condylar and patellar lesions. They categorised the results as excellent (no pain, swelling or locking with strenuous activity), good (mild aching with strenuous activity, but no swelling or locking), fair (moderate pain with strenuous activity and occasional swelling, but no locking) or poor (pain at rest and locking). Patients with femoral condylar transplants had decreased pain in the knee, swelling and crepitation, and locking had been abolished. Biopsies showed that 11 of the 15 femoral transplants had the appearance of hyaline cartilage. Two years after transplantation, 14 of the 15 patients with femoral condylar transplants had good-to-excellent results. The two patients followed for the longest period had excellent results at 55 and 59 months after implantation. For the seven patients with patellar transplants, the outcome was graded as excellent or good in two, fair in three and poor in two at a mean follow-up of 36 months. Five of the seven had improved knee function as indicated by the absence of locking. Peterson et al. evaluated the durability of ACI grafts in either the femoral condyle or patella in 61 patients, with a mean follow-up of 7.4 years. At two years, 50 of the 61 patients (82%) had good or excellent results and at further follow-up for five to 11 years, 51 of the 61 had good or excellent results.

Similar results were published in 2001 by Micheli et al. who had a success rate of 94% in a multicentred study involving 50 patients treated by ACI, with a minimum follow-up of 36 months. Henderson et al. described 230 patients with either femoral, trochlear or patellar lesions. They found that it gave a durable long-term option for repair of the articular cartilage with good to excellent results in 84% of cases for up to 11 years after implantation.

In 2002, Browne et al. compared ACI with microfracture with 23 patients in each group. Those treated by ACI had a statistically significant improvement in their symptoms compared with those managed by microfracture.

In 2003, Peterson et al. evaluated ACI for the treatment of osteochondritis dissecans in 58 patients at follow-up for between two and 10 years, with a 90% successful clinical result. In 2003, Horas et al. assessed 40 patients with lesions of the weight-bearing area of the femoral condyle and found that at two years after operation the defects showed complete and mechanically stable surfaces in all the patients.

Bentley et al. in a randomised, prospective trial, compared ACI with mosaicplasty in 100 consecutive patients. The results were excellent or good in 88% of the patients treated by ACI compared with only 69% of those who had mosaicplasty. Arthroscopic assessment of the lesions by the ICRS grading system, at one year showed a grade-I or grade-II appearance in 84% of the ACI-treated patients compared with only 35% of those with mosaicplasty.

In 2005, Fu et al. noted their superior results with ACI compared with debridement in a cohort study carried out over a period of three years in 54 and 42 patients, respectively.

Knutsen et al. in a randomised trial compared the outcome in 40 patients treated by microfracture and in 40 treated by ACI. Both methods gave satisfactory results in 77% of the patients at five years. There was no significant difference in the clinical and radiological results between the two groups and no correlation between the histological findings and the clinical outcome. They concluded that further long-term follow-up would be crucial to determine whether there was any difference between the two techniques.

In 2008, Saris et al. published the results of another randomised trial examining the differences between ACI and microfracture. There were 57 patients randomised to ACI compared with 61 for microfracture. One year after treatment, ACI was associated with a tissue regenerate which was superior to that of microfracture. The short-term clinical outcome was similar for both groups. However, the authors used characterised chondrocytes, cells expressing a specific gene profile predictive of greater capacity to form hyaline-like cartilage in vivo. This gene profile aimed to preserve phenotypic characteristics and biological activity unlike in conventional ACI in which cells dedifferentiate and lose chondrogenic capacity. The superior phenotypic profile of characterised chondrocytes may lead to an improved structural outcome, as this study suggests. Nevertheless, long term follow-up is needed to assess whether this translates to improved clinical benefit.

Browne et al. in 2005, reported an improvement of 71% at five years in a difficult group of patients with previous surgical procedures, large lesions and poor function.

Mithöfer et al. investigated the use of ACI in high-level athletes. A total of 45 football players underwent ACI, with a maximum follow-up of 41 months. Good to excellent results were achieved in 72%. This improved to 85% in players with single cartilage lesions and to 93% in those with isolated lesions in the medial femoral condyle.

In 1998, Minas evaluated the health economics of the ACI technique by examining the efficacy of treatment and the quality of life in 44 patients who had undergone the procedure and calculated the mean cost per additional quality-adjusted life year. They concluded that ACI improved the quality of life of patients and was a cost-effective treatment for cartilage lesions.

Autologous chondrocyte implantation at the Royal National Orthopaedic Hospital: the experience of nine years
Our prospective study was performed to evaluate the repair of articular cartilage using ACI carried out within a single centre under the guidance of the senior author (GB) and ethical approval had been obtained. A periosteal flap technique was used until 2003 when MACI was developed. Since then, patients have been randomised to ACI-C or to MACI.
Since 1998, all patients undergoing ACI or MACI by one surgeon (TWRB) were entered into this prospective study. There were 332 patients (176 males, 156 females) with a mean age of 33.4 years (15 to 52). The primary indication for surgery was persisting pain resulting from an isolated osteochondral defect greater than 1 cm² in the articular surfaces of the knee. The mean follow-up was 32 months (12 months to 9 years). A total of 101 patients underwent ACI and 231 had MACI.

Trauma, osteochondritis dissecans and chondromalacia patellae were the principal indications for surgery, with a large proportion of patients having previously undergone other surgical treatments (Table I).

Clinical assessments were carried out at 12 weeks, at six and 12 months and then annually. The subjective and objective clinical outcomes were recorded. Arthroscopy and biopsy were carried out at 12 months after implantation.

Patients with instability, abnormal joint alignment, osteoarthritis and inflammatory joint disease were excluded. Since 2003, patients have been randomised to ACI or MACI as part of an ongoing multicentre clinical study. They all entered a structured rehabilitation programme.

In addition to the normal pre-operative investigations, all the patients were assessed before ACI using the following validated clinical scoring systems: 1) the modified Cincinnati rating score (MCRS) (0 to 100)⁴¹; 2) a visual analogue score (VAS) (0 to 10); 3) the Bentley functional rating score (0 to 4)⁴²; 4) the Lysholm-Gillquist score (0 to 100)⁴³; 5) the patient functional outcome score (0 to 10) and 6) the score of Brittberg et al.¹⁰ (poor, fair, good or excellent).

The annual functional outcome was assessed using a postal questionnaire of the same scoring systems. Clinical assessment was also performed annually in the outpatient department. The response rate was 97% throughout all annual patient assessments. Patients lost to follow-up were allocated poor or low outcome scores.

The size of the osteochondral defects was similar in both the ACI and MACI groups, with three patients having dual defects treated by ACI and nine with dual defects treated by MACI. The mean area of the osteochondral defect repaired using ACI (3.5 cm², range 1.0 to 7.0) was not significantly different (unpaired t-test, p > 0.05) from that treated by MACI (4.2 cm², range 1.0 to 12.2).

Results

Clinical outcome. There was a sequential annual statistically significant improvement in the MCRS score for ACI and MACI (paired t-test, p < 0.0001) in comparison with the pre-operative level (Fig. 2). Whilst at one year ACI showed a significantly better MCRS compared with MACI (unpaired t-test, p = 0.021), there was no significant difference (unpaired t-test, p > 0.05) between the techniques in subsequent years.

In comparison with the pre-operative VAS score, both ACI and MACI showed sequential significant improvements (paired t-test, p < 0.0001; Fig. 3). There was no significant difference (unpaired t-test, p > 0.05) between the techniques in subsequent years.

In comparison with the pre-operative VAS score, both ACI and MACI showed sequential significant improvements (paired t-test, p < 0.0001; Fig. 4). There was no significant difference (paired t-test, p < 0.0001) in the VAS between ACI and MACI.

There was no significant difference (unpaired t-test, p > 0.05) in the Bentley functional rating score between ACI and MACI, although both techniques showed significant and sequential improvements (paired t-test, p < 0.0001) in comparison with their pre-operative scores (Fig. 4).

All patient functional outcome scores improved significantly (paired t-test, p < 0.0001) in comparison with their respective mean pre-operative scores (Fig. 5). Comparing the two techniques, ACI had a better patient functional outcome score at one year in comparison with MACI (unpaired t-test, p = 0.0454) but there was no significant difference (unpaired t-test, p > 0.05) in subsequent years. Similar to the patient functional outcome score there were sequential annual improvements in the Lysholm-Gillquist scores for both ACI and MACI, with ACI being significantly
better at one year (unpaired $t$-test, $p = 0.007$), but with no significant difference (unpaired $t$-test, $p = 0.89$) in the techniques at two or three years (Fig. 6).

The Brittberg rating enabled patients to score knee function subjectively as poor, fair, good or excellent. Figure 7 shows the sequential results for both the ACI and MACI techniques, with the responses being grouped as excellent or good compared with fair or poor. Continued sequential increases in good or excellent responses were observed with both techniques, with a corresponding reduction in adverse assessments (paired $t$-test, $p < 0.001$). The rate of improvement of beneficial and the rate of decline of adverse responses, using the trendline gradient, was three times greater for MACI than for ACI.

Histological examination. A total of 185 patients had a post-implantation biopsy at a mean time of 14.8 months (3 to 55). This was routinely scheduled at 12 months, but realistically took place at various time points because of National Health Service restraints. The results are summarised in Table II. Examples of the varying histological outcome are shown in Figure 8. Some evidence of the presence of hyaline tissue, either hyaline-like or mixed hyaline and fibrocartilage, was seen in 85 (46%) of the biopsies.

Discussion

In our study when considering the modified Cincinnati and Lysholm-Gillquist scores, continued improvements were noted in knee function. Significant improvements were
seen in all the scores compared to those before operation (paired t-test, p < 0.001) with annually maintained improvement for up to nine years.

The technical ease and practical advantages of MACI have led to its preference by some surgeons, although the long-term durability and survivorship of the graft are currently unknown. Although our results suggest that it has a slightly better rate of clinical improvement in comparison with ACI, further clinical and histological evidence will be required to validate each technique. Our histological assessment suggested that later biopsies are more likely to show hyaline-like tissue, which strongly supports the idea that the repair improves in quality and remodels with time.44

Our results from this prospective study were encouraging and provided further evidence of the benefit in the medium term of transplanting autologous chondrocytes to areas of osteochondral defects.

The future of autologous chondrocyte implantation

The medium-term results of ACI using either a periosteum (ACI-P) or a collagen type-I/III (ACI-C) membrane appear to be encouraging, but long-term results are awaited. The fundamental question of the importance of the cultured chondrocytes in the process of repair needs answering. A prospective, randomised blinded study is underway at our centre, which will compare MACI, which we have shown to be as effective as ACI-C at three years, against microfracture covered with type-I/III collagen membrane, autologous matrix-induced chondrogenesis. This will allow a direct comparison to be made between techniques of marrow stimulation and the use of cultured chondrocytes. Improvements in cell engineering, such as the arthroscopic implantation of cells, and the delivery of the chondrocytes on a three-dimensional matrix-gel are also in progress.

There is evidence that the process of repair can be influenced and enhanced by bone morphogenetic proteins (BMPs). These are members of the transforming growth factor-β (TGF-β) super family.45 They are multifunctional growth factors and stimulate cells to proliferate.46 They also have two other functions. They are required for the formation of pre-cartilaginous condensations from the mesenchymal precursors and for the differentiation of precursors into chondrocytes. It is known that BMPs -2, -4, -6, -7, -9 and -13 stimulate the synthesis by adult chondrocytes of type-II collagen and aggrecan, which are the main constituents of the cartilage matrix. Local delivery of BMPs by genetically-engineered stem cells has been shown to enhance chondrogenesis and the repair of articular cartilage in animals,47 but no human studies have yet been undertaken. This is because enhanced BMP activity has been observed in some tumour cells, such as in carcinoma of the breast, and hence enhancement with BMPs may have the potential for the initiation of tumours.48

BMPs also stimulate the chondrogenic differentiation of stem cells, another important avenue of research in the repair of cartilage. It has been shown that BMP-4 and other BMPs can induce embryonic stem cells and mesenchymal progenitor cells to undergo chondrogenesis. The mesenchymal differentiated chondrocytes induce cartilage repair at a
similar level as that of ACI within four weeks of transplantation in vivo. Unlike MACI this procedure does not require the use of collagen scaffolds and is currently under investigation.\cite{49}

Assessment of the defects both before and after operation will improve with the aid of MRI. With advances such as the use of delayed gadolinium-enhanced scans,\cite{30} more information will be available regarding the localisation and
size of the defect, as well as the histological structure of the graft without the need for invasive surveillance.

Untreated, articular cartilage defects of the knee may cause pain, disability and ultimately progress to osteoarthritis. The aim of any technique of cartilage repair is to produce a joint which moves fully without pain with a surface which is durable for the medium and long-term. If a durable repair can be achieved this may prevent further deterioration of the local cartilage and the subsequent development of osteoarthritis.

ACI has become a popular technique for treating isolated chondral defects of the knee and has now been performed on an estimated 10,000 patients worldwide. Most groups have reported good to excellent clinical and histological results using this technique, but there is still scepticism amongst many surgeons about its effectiveness, the type of repair produced and its durability. Which patients should receive it and the timing of its use in relation to other techniques such as microfracture remains uncertain.

From a review of the available literature and our experience of the clinical outcome for isolated chondral defects of the knee using ACI we can make the following conclusions: There is no current evidence to justify treatment in asymptomatic, small (< 1 cm²) chondral defects of the knee. Adult patients with symptomatic full-thickness defects have poor results if not treated. Instability and malalignment require correction. Smaller, well-contained lesions may be suitable for microfracture, but for patients who do not respond to microfracture, ACI offers a satisfactory alternative salvage procedure. ACI-C leads to a statistically significant improvement in objective and patient-reported clinical outcomes and produces a durable outcome for as long as nine years. The clinical results of the ACI-C and MACI techniques are comparable and the percentage of hyaline cartilage at biopsy appears to improve with time. Finally, the location of the lesion will affect the outcome of the intervention.

A review of the literature shows that there is some variation in the pre-operative assessment and in the regimes of post-operative rehabilitation. However, all these studies show significant improvement in function after ACI and improvement over other methods of management. Further research will enhance our understanding of the molecular and cellular events involved in the repair of cartilage and the clinical characteristics which influence it, eventually improving the functional results.

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References


