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Operative Treatment of Knee Cartilage Injuries: A Review of the Current Literature on Non-Cell-Based and Cell-Based Therapies

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Review Article

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ABSTRACT

Aims: Cartilage is frequently damaged through injury and disease but shows little or no capacity for repair. Injuries that extend to the subchondral level show some capacity for repair due to the release of bone marrow derived mesenchymal stem cells. Focal articular cartilage defects are challenging clinical problems that may progress to more generalised lesions. We reviewed the literature to analyse the results of available non-cell-based and cell-based strategies for the repair of articular cartilage defects in the knee.
Study design: Review Article
Place and Duration of Study: University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, Middlesex, HA7 4LP, United Kingdom
Methodology: We reviewed the literature to identify studies on the use of non-cell-based and cell-based strategies for the repair of articular cartilage defects in the knee.
Results: Repair techniques that do not utilise cell therapy include bone marrow stimulating techniques such as microfracture that is effective in small well-contained lesions and has the advantages of being performed arthroscopically as a single stage and cheaper costs compared to cell-based therapies. It also associated with no donor site morbidity unlike mosaicplasty, and perichondrial or periosteal grafting. The evidence suggests that none of the techniques described above consistently produce

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durable results. There are encouraging mid-term results with Autologous Matrix Induced Chondrogenesis (AMIC) procedures in small number of patients. Although microfracture is appropriate for smaller cartilage defects, Autologous Chondrocyte Implantation (ACI) and Matrix-carried Autologous Chondrocyte Implantation (MACI), as well as other cell carrier systems, are currently used to treat larger full thickness chondral defects in the knee. Although the results are fairly similar, MACI and procedures using other cell carrier systems are amenable to be performed arthroscopically or through a more limited approach. There are a small number of studies using mesenchymal stem cells with promising early results bur further *in vitro* and *in vivo* studies are needed before this treatment becomes more routinely available.

Conclusion: Focal articular cartilage defects are challenging clinical problems that progress to more generalised lesions. Only cartilage injuries that extend to the subchondral level show some capacity for repair due to the release of bone marrow derived mesenchymal stem cells. Bone marrow stimulating techniques such as microfracture are effective in small well-contained lesions (<2cm^2) and have the advantages of being performed arthroscopically as a single stage and cheaper costs compared to cell-based therapies. Mosaicplasty, and perichondrial or periosteal grafting are associated with donor site morbidity. Longer term studies on AMIC may help define the role for this procedure. The best form of non-cell-based treatment for focal articular cartilage defects in the long term is still unknown. ACI and MACI, as well as other cell carrier systems, are currently used in clinical practice to treat larger full thickness chondral defects in the knee. There are a small number of studies using mesenchymal stem cells and further *in vitro* and *in vivo* studies are needed before this treatment is optimised.

Keywords: Microfracture; AMIC; mosaicplasty; carbon fibres; osteotomy; ACI; MACI; mesenchymal stem cells; clinical studies;

1. INTRODUCTION

Articular cartilage has a unique structure and function. It forms the articulating surface of diarthrodial joints and provides friction-free load-bearing on joint surfaces, hence allowing smooth movement without pain. However, when articular cartilage gets damaged, the properties change due to in innate ability for self repair.

The response of cartilage to injury differs from this classic response because of two important features of the structure of cartilage. The most important is its avascular status (Mankin, 1982). The second difference is that the chondrocytes are literally imprisoned in a mesh of collagen and proteoglycan, unable to migrate to the injury site from adjacent healthy cartilage. Even if they were able to turn their synthetic engines on in an effort to replace damaged matrix, they cannot get to where they are needed. These conditions will be different if the cartilage injury penetrates through the subchondral plate, providing a pathway to the highly vascular bone. In this injury, because of the participation of the vascular system, the repair response is much more similar to that seen elsewhere in the body. Descriptions of the attempt of articular cartilage to heal itself after injury have typically followed two pathways, one detailing the events after a superficial injury to articular cartilage,

and the other involving a deep, full-thickness injury through the subchondral bony plate (Buckwalter et al., 1997).

It is clear that not all patients with chondral damage in the knee require treatment. Shelbourne et al. (2003) had demonstrated that cartilage injuries noted at the time of anterior cruciate ligament reconstruction do not affect clinical outcome at a mean of 8.7 years. Furthermore, even radiological evidence of osteoarthritis does not necessarily correlate with symptoms (Messner and Maletius, 1996). The results from these two studies beg the question why we should treat chondral lesions? This question is nicely answered by Linden who published an observational study of 58 patients (76 knees) who had osteochondritis dissecans (OCD) at mean follow-up of 33 years. Only 9% of the 23 children developed arthritis compared with 81% of adult-onset osteochondritis dissecans patients. This suggests that OCDs in adults should be treated more aggressively to prevent early onset osteoarthritis.

The treatment for articular cartilage damage in the knee has developed considerably over the past few decades but debate persists about the best form of treatment. The rapidly developing technologies in cartilage repair are testament to the challenging problem that chondral and osteochondrall defects (OCDs) pose. A variety of surgical options exist for the treatment of osteochondral defects in the knee. A number of techniques endeavour to replace the defect with hyaline cartilage, including using osteochondral allografts, osteochondral autografts, or mosaicplasty. To date, none have been proven to provide a long term and reproducible improvement in pre-operative function, and concerns such as disease transmission and donor-site morbidity remain. The challenge of recreating the special properties of hyaline articular cartilage is still ongoing, since it is so resilient and non-uniform. A cellular approach to the treatment of cartilage damage in the knee appears an attractive proposition, since it offers the best possibility of replacing damaged articular cartilage with hyaline-like cartilage (Punwar and Khan, 2011; Jaiswal et al., in press). This review will also discuss the origins of cell therapy for the treatment of osteochondral defects in the knee, namely in the form of autologous chondrocyte implantation and also look to the future and current literature regarding the use of mesenchymal stem cells. This review will focus on the efficacy of all the surgical techniques including cellular therapy for the treatment of chondral and OCDs of the knee.

2. METHODOLOGY

A thorough literature review was conducted and articles relating to the use of non-cell-based and cell-based strategies for the treatment of articular cartilage defects of the knee were identified. The searched primarily focused on common treatment options including debridement, microfractures, mosaicplasty, perichondrial grafts, carbon fibres, osteotomies, Autologous Chondrocyte Implantation (ACI), Matrix-Carried Autologous Chondrocye Implantation (MACI; Verigen, Leverkusen, Germany), and mesenchymal stem cells.

3. RESULTS

3.1 Debridement

Cartilage in and around a symptomatic chondral defect is abnormal. Matrix metalloproteinases are produced in response to mechanical overloading (Blain et al., 2001; Honda et al., 2000) and this has a damaging effect on the opposing surfaces and

surrounding cartilage. As demonstrated by Hubbard, simple excision of surrounding damaged caretilage can give long term benefit for up to 5 years. The debridment was performed on knees with single lesions of grade 3 or 4 of the medial femoral condyle. There was some deterioration in the first two years, but 65% of the knees were free from pain at five years (Hubbard, 1996).

In this study, it was recommended that patients should be selected on the basis of a chondral defect combined with local tenderness. His surgical technique involved the careful removal of all loose cartilage from the defect with the use of a selection of punches. No powered instruments were used and no attempt was made to abrade the surface of the defect or the drill the condyles. In this prospective randomised trial arthroscopic lavage was used as the control. The debridement group had significant improvement when compared with lavage as measured by the Lysholm score.

There is no doubt that there is a place for debridement as an initial surgical procedure for the treatment of OCDs in the knee but there is conflicting evidence for the use of debridement in widespread osteoarthritis of the knee (Moseley et al., 2002; Jackson et al., 2003). There has been a gradual decline in the use of arthroscopic debridement and washout for the treatment of generalised osteoarthritis in the knee and this mainly has been due to funding issues from primary care trusts.

3.2 Microfracture

Microfracture is one form of marrow-stimulating technique where the chondral lesion is exposed to material moving from bone cavity through the subchondral plate. It combines accurate debridement of damaged and unstable articular cartilage with the creation of multiple holes in the subchondral bone of the defect.

This procedure was pioneered by Richard Steadman over 15 years ago (Steadman et al., 1997, 2001, 2003, 2003, Miller et al., 2004). An arthroscopic awl is used to make the holes in the defect 3 to 4 mm apart, and ensuring the subchondral plate is kept intact. The principle behind this technique is the infiltration of pluripotential mesenchymal stem cells from the vascular subchondral bone into the defect forming stable repair tissue which is mainly fibrocartilaginous (Steadman, 2001).

As with all soft tissue knee procedures, the rehabilitation protocol is of paramount importance in determining outcome. Most surgeons advocate early mobilisation of the knee with continuous passive motion. In addition, weight bearing should be reduced for at least four weeks (Steadman, 1997).

Since its first description, microfracture has consistently demonstrated improved outcomes in the treatment of cartilage damage in the knee (Steadman et al., 2003), and has been recently described in the shoulder (Millett et al., 2009) and hip (Crawford et al., 2006.).

Hunziker has described acceptable clinical results with the use of marrow-stimulation techniques up to five years and though results do decline thereafter (Hunziker, 2002). Conversely, Steadman et al has published outcomes of microfracture demonstrating 80% of patient satisfaction rates seven years following surgery (Steadman, 2003). They also found that patients aged less than 35 years improved more than those aged between 35 and 45 years. It has to be stated that the chondral lesions in this cohort of patients were relatively small (average 2.8cm^2), and there were no histological analysis performed. In 20 biopsies

performed 2 years after microfracture, 11.4% had predominantly hyaline cartilage and 17.1% a mixture of fibrocartilage and hyaline cartilage within them (Knutsen et al., 2004).

Comparison of results from various studies is made difficult by the heterogeneity of patient demographics, lesion characteristics, degree of widespread joint degeneration and the use of simultaneous procedures. The most commonly used outcome scales used in clinical studies are the Lysholm score and the Tegner activity score and in a recent systematic review of the microfracture technique, improved knee function were reported in 24 studies (Mithoefer et al., 2009). The improvement in quantitative knee scores occurred as early as 6 months and was maintained in most studies until 24 months, but the results tended to decline after this period. Long term clinical results (> 5 years) have been reported in 5 studies. 67% to 86% of patients reported improved knee function at a mean of 6 to 7 years following surgery. Steadman's study had the longest average follow up of 11 years, and only 32% of patients were completely pain free with a further 54% describing mild pain. In seven studies, 47 to 80% of patients reported a deterioration in the initial improvement in function approximately 18 to 36 months after microfracture. Nevertheless, the scores were still higher than the pre-operative status (Blevins et al., 1998; Gobbi et al., 2005; Gudas, 2005; Kreuz et al., 2006; Kreuz and Steinwachs et al., 2006; Mithoefer, 2006).

A number of factors have shown to affect outcome. Younger patients appear to have better knee function following this procedure (though the threshold in studies varies between 30 and 40 years of age) (Miller et al., 2004; Gudas et al., 2005; Kreuz et al., 2006; Mithoefer, 2006). Having the microfracture procedure performed within 12 months of diagnosis is associated with better clinical results as well as the lesion size being less than $4cm^2$ (Gill, 2000, Mithoefer et al 2006). In demanding athletes lesion sizes of less than $2cm^2$ is associated with higher rate of return to physical activity (Gudas, 2005, Mithoefer, 2006). A high body mass index (BMI), particularly a BMI > 30 is associated with inferior knee scores after microfracture (Mithoefer et al., 2005). When microfracture is performed as primary procedure rather than as a salvage procedure the results are better (Gill, 2000; Mithoefer, 2006). Finally, those patients with higher pre-operative knee activity scores (Tegner score of > 4) had better results following surgery (Blevins et al., 1998; Knutsen et al., 2004; Mithoefer, 2006).

In Steadman's original description there were no perioperative complications in 1,275 patients (Steadman et al., 1997). Similarly, there were no adverse results reported in two randomised controlled trials (Knutsen et al., 2007; Gudas et al., 2005) and one observational study of 350 patients (Miller et al 2004). The rate of minor local infection and below knee deep vein thrombosis can be as high as 2% (Gobbi et al., 2005; Gudas et al., 2005; Knutsen et al., 2007) with moiré serious adverse effects occurring in 13% (Rodrigo et al., 1994). The rate of failure after microfracture is highly variable but appears to be time dependent. Early revision rates (less than 2 years) were 2.5% but increased to 31% two to five years after surgery (Steadman et al., 1997; Gobbi et al., 2005).

3.2.1 Autologous matrix induced chondrogenesis (AMIC)

More recently improvements have been made using autologous matrix induced chondrogenesis (AMIC) procedures which have shown better early results (Steinwachs et al., 2008), but medium- and long-term results are not yet available. The AMIC technique is a second generation marrow stimulation procedure that combines microfracture with a collagen Type III/I membrane (Geistlich Pharma, Wolhusen, Switzerland) and fibrin glue. It enables treatment of larger defects and has the advantage of not requiring any cell-based

procedures as discussed below. Early results suggest that AMIC is particularly suitable for treating retropatellar cartilage defects. In addition, AMIC combined with platelet-rich plasma gel, the so called AMIC plus technique, has also been described for patellar cartilage defects in the knee (Dhollander et al., 2011). Although early clinical results in this pilot study were encouraging, they were not corroborated with radiological findings.

In 2010, Gille et al. published a prospective study evaluating the medium-term results of this technique. Thirty-two Outerbridge grade IV chondral lesions with a mean defect size of 4.2 cm^2 in 27 patients with a mean age of 37 years were treated with AMIC and evaluated at 5 years. Significant improvement of clinical outcome scores was observed at 12 months and 24 months postoperatively. MRI analysis showed moderate to complete filling with a normal to incidentally hyperintense signal in most cases. The authors concluded that AMIC is an effective and safe method of treating symptomatic full-thickness chondral defects of the knee in appropriately selected cases. However, further studies with long-term follow-up are needed to determine whether the grafted areas maintain structural and functional integrity over time.

3.3 Mosaicplasty

Hangody originally described this procedure which is also known as osteochondral autografting (Hangody, 1997, 2003). A cylindrical cutting device is used to harvest osetcochondral plugs from non-weight bearing areas of femoral condyles at the level of the patellofemoral joint. Cutting devices can come in a variety of diameters (2.7, 3.5, 4.5, 6.5, and 8.5 mm) to create plugs of different sizes to maximize filling of the osteochondral defect. This procedure is usually performed through a mini-arthrotomy but smaller defects can be done arthroscopically (Solheim et al., 2010). Lesions in the patellofemoral joint require subluxation of the patella and this can be quite painful in the postoperative period (Hangody et al., 2004). There are certain indications and contraindications.

The indications are

- Focal chondral and osteochondral defects of weight-bearing articular surfaces of the knee
- Defects of other diarthrodial surfaces of the talus, humeral capitulum, and femoral head
- Age of less than fifty years
- Diameter of defect ideally between 1-4 cm^2
- Concurrent treatment of instability, malalignment, and meniscal and ligament tears essential
- Patient compliance (i.e., compliance with weight-bearing limitation) critical

The absolute contraindications are

- Tumor, infection, generalized or rheumatoid arthritis
- Osteoarthritis
- Lack of appropriate donor area
- Age of greater than fifty years
- Defect larger than 8 cm^2
- Defect deeper than 10 mm
- Noncompliant patient

Relative contraindications are

- Age of between forty and fifty years
- Defect between 4-8 cm^2
- Mild osteoarthritic changes

One of the main advantages of this procedure is that it can be performed in a single stage and the defect can be filled immediately. However the size of the defect to be treated is limited by the amount of plugs that can be harvested from non-weight bearing areas and donor site morbidity. For this reason Hangody recommends that lesions greater than 4cm^2 should not be treated by this method (Hangody et al., 2004). There are also concerns regarding whether the subchondral layer is truly reconstituted. Furthermore, the lack of lateral integration that occurs in most patients raises the possibility of penetration of the subchondral layer by synovial fluid and cyst formation. Perpendicular access to the cartilage surface by cylinder cutters is required for this technique and this makes treatment of defects of the tibial plateau difficult.

Comparison of efficacy across published studies is difficult due to the different outcome measures used in the studies. In a randomised controlled trial of 100 patients that had either undergone mosaicplasty or autologous chondrocyte implantation, there were no statistically significant differences at a mean follow up of 19 months (Bentley et al., 2003). However, the difference in proportion of excellent and good results was nearly 20% suggesting that the study was underpowered. All seven poor results were in the mosaicplasty group. In 10% of patients (4/42) the transplanted plugs were in situ, but the tissue between them was not covered with continuous repair tissue. In three cases (7%) the graft had disintegrated and in one case (2%) the articular cartilage at the margins of the defect had broken down.

Mosaicplasty was successful in 77% of cases (n=69) 12 months following surgery (Solheim et al 2010). However the Lysholm score had deteriorated at the 5-9 year follow-up. A significant negative correlation was found between Lysholm score at final follow-up and the age of the patient at the time of the surgery ($r=-0.29$, $p=0.016$). There was no such relationship with the sex of the patient, duration of symptoms or the size of the grafted area.

The largest single series of mosaicplasty to date is that of Hangody and Fules (2003) who reported the results of operations on 831 knees (597 femoral condyles, 118 patellofemoral joints and other sites) at up to ten years post-operatively. All patients were under 50 years of age. Only a third of patients had localised osteochondral defects, the remainder having localised grade III or IV degenerative cartilage lesions. Furthermore, 85% of procedures had concomitant surgical interventions (e.g. cruciate ligament reoncstruction, realignment osteotomies, meniscal surgery, or patellofemoral realignment). Good or excellent results were reported in 92% of patients with femoral condyle lesions, 87% of tibial plateau lesions and 79% of who underwent patellar or trochlear mosaicplasty. This paper does not give the mean time to follow-up and did not discuss the survival of osteochondral grafts in those patients with the longest follow-up. Smaller case series have similar short term results (Bentley et al., 2003, Hangody et al., 1998, Jakob et al., 2002) at 6 to 12 months though Hangody's long term results have not been reproduced elsewhere (Hangody et al., 2003).

In the large series by Hangody, the rate of deep infection was less than 1% (4/831) with similar rates of thromboembolic complications (2/831). There was higher rate of painful haemarthrosis (36/831, 4%). In another smaller series (n=52), 10% of patients complained of locking. The rate of deep infection was 2%, as was severe haematoma and joint stiffness (Jakob et al., 2002). In the most recent case series, the rates of haemarthrosis and infection were similar however the rate of re-operation (second arthroscopy) due to insufficient improvement in symptoms was high (33%, 23/69 patients). In six of these patients the mosaicplasty was not in tact due to loss of one or transplanted grafts. Another full thickness chondral lesion adjacent to the mosaicplasty was seen in another six patients (Solheim et al., 2010).

3.4 Perichondrial Grafts

This technique originated from a rabbit model, in which rib perichondrium was used to repair full-thickness defects in the femoral condyle. The quality of repair was then evaluated histologically and biochemically at six and twelve weeks after grafting. Unacceptable results were obtained in 50 per cent of the rabbits. These failures were due to condylar fracture in 20 per cent, failure of graft attachment in 20 per cent, and infection in 10 per cent. Homminga et al. first described the use of this technique in humans. Eighteen out of thirty patients were completely symptom free, with the mean knee score increasing from 73 preoperatively to 90 1 year after surgery (Homminga et al., 1990). At mean of 24 months after surgery, the results were only available for 14/30 patients, and the postoperative scores were maintained (Mean knee score was 87).

A longer term study (mean follow up 52 months) in 88 patients revealed good results in only 38% using the Hospital for Special Surgery score (Bouwmeester et al., 1997). In a histological analysis of 22 biopsies taken after perichondrial grafting, tissue with a hyaline morphology of over 50% was found in only six biopsies (27%) (Bouwmeester et al., 1999).

3.5 Carbon Fibres

Minns described the use of filamentous carbon fibre for the repair of defects of the articular cartilage in rabbits. The inert carbon-fibre implants, first used in rod form and then as woven pads, served as a scaffold for the ingrowth of fibrocartilage and enhanced the ultimate durability of the fibrocartilaginous surface after making drill holes into the femoral condyle (Minns et al., 1982). The success with this model encouraged clinical use of the implant. In a clinical review of 96 patients, 79% had experienced an improvement in pain and functional activities scores up to five years after surgery. There were no complications. Two more recent studies have analysed the use of carbon fibre implants either in the patella (Meister et al., 1998) or the femoral condyles (Nicholson et al., 1998). Whilst there was a 61% success rate in eighteen patients with lesions in the femoral condyles (Nicholson et al., 1998) the results were poor in treating defects of the patella (41% satisfaction rate in 28 patients).

No systematic histological study has been reported but, in failed implants, poor quality fibrous tissue with carbon fibre fragmentation is seen over the pads. The main disadvantage of carbon rods is the introduction of a nonabsorbable material deep to the subchondral bone. In early osteoarthritis, Brittberg, Faxen and Peterson had 83% success in 37 patients who were studied prospectively (Brittberg et al., 1994). This may, therefore, be the best indication for the use of carbon fibre, where there are degenerative changes present and when knee replacement would be the next form of treatment.

3.6 Osteotomy

Patients with focal articular cartilage damage in the medial compartment of the knee are at moderate risk of progression to arthritis (Linden 1977; Messner et al., 1996) and if there is varus malalignment the risk of progression is significantly increased (Sharma et al., 2001). Furthermore, biomechanical studies have demonstrated elevation in cartilage pressures in the medial compartment under loading in the varus aligned knee. Due to these reasons, patients with chondral lesions and varus malalignment have not achieved good results with cartilage restorative procedures alone (Minas and Peterson, 1999).

High tibial osteotomy (HTO) has become a well established method for treating symptomatic medial unicompartmental osteoarthritis. The aim is to shift the loading axis from the degenerated medial compartment to the intact lateral compartment, with the goal to relieve pain and progression of osteoarthritis. The landmark paper by Conventry et al. stated that the 10-year survival rate was significantly better if at least 8 degrees of valgus angulation could be achieved post-operatively. Hence these findings have led to the post operative goal of 8-10 degrees of valgus correction. A more recent biomechanical has revealed complete unloading of the medial compartment at between 6 and 10 degrees of valgus, and that contact pressure is equally distributed between the medial and lateral compartments for alignments of 0 to 4 degrees of valgus (Mina et al., 2008).

HTO can be performed in two ways; lateral close-wedge osteotomy or medial open-wedge osteotomy. There have been several problems documented regarding close-wedge osteotomies:

- The degree of correction is difficult to control and over- or under-correction can be easily achieved (Dugdale et al., 1992; Hernigou et al., 1987).
- Long term results have frequently deteriorated with time (Insall et al., 1984, Naudie et al., 1999; Rinonapoli et al., 1998)
- Inferior results of total knee arthroplasty (TKA) have been reported after closing-wedge HTO (Katz et al., 1987; Cameron and Park 1996) with reports suggesting it is easier to convert to medial opening-wedge osteotomy to TKA (Franceschi et al., 2008)
- Finally, there is a higher incidence of peroneal nerve palsies with closing-wedge osteotomies (Noyes et al., 2006)

The early and midterm results of chondral resurfacing (abrasion and microfracture) with medial opening-wedge osteotomy are encouraging. This technique started in Colorado in 1995 and the first cohort of patients (n=38) had reported an increase in Lysholm score from 43.5 to 78 at mean of 45 months after surgery (Sterett and Steadman, 2004). At the same institute, a Kaplan-Meier analysis revealed 91% survivorship at 7 years with the end point being knee arthroplasty (Sterett et al., 2010). In the last study, it was also discovered that patients with medial meniscus injury at the time of surgery were 9.2 times more likely to undergo arthroplasty than patients without. These results are in keeping with another study with shorter follow-up (Miller et al., 2007).

Investigations into the efficacy of chondral resurfacing and HTO to treat more widespread degenerative changes have been inconclusive. There was improved cartilage regeneration on histology in patients who had abrasion arthroplasty and HTO than patients who had HTO alone (Schultz and Gobel et al., 1999). Though there was improved walking distance and knee extension in the latter group there was no significant difference in the clinical scores. Similar results were seen in another study (Akizuki et al., 1997).

A combination of cell therapy and HTO represents a logical step to improve results in the treatment of this difficult condition and there is very little research at present. In a small study, cultured autologous bone marrow stem cells were added to the tibial plateau of 12 patients and the results were compared with a control group of 12 patients who had oseotomy alone (Wakitani et al., 2002). Twelve months following surgery, better histology was obtained in the stem cell group but the clinical results were similar. In a case series, 12 patients with localised medial compartment arthritis and varus malalignment had undergone Matrix-Carried Autologous Chondrocyte Implantation (MACI) and HTO. Six minute walk test

and knee injury and osteoarthritis outcome score indicate significantly improved functional capacity at six months and one year following surgery in all patients. At a slighter longer follow-up of 28 months, arthroscopic implantation of autologous chondrocytes and HTO resulted in significant improvement in 7/8 patients (Franceschi et al., 2008).

3.7 Periosteal Grafts

The use of whole tissue periosteal transplant is attractive as it meets the three requirements for tissue engineering; a source of cells, a scaffold for delivering and retaining them, and a local source of growth factors. Perisoteum has chondrogenic potential due to the cambium layer containing chondrocyte precursor cells that form cartilage during limb dvelopment and growth in utero and also during fracture healing in adult life. O'Driscoll was among the first researchers to describe animal experiments showing that perosteal grafts placed on articular cartilage defects can produce new cartilage and a congruent joint surface and considerable work has been done since (O'Driscoll and Salter 1984; Singh et al., 2009; Hui et al., 2004). This repair process can be enhanced when adding growth factors (Olivos-Meza et al., 2010).

In a study of 26 patients with OCD of the patella, 17 patients had excellent or good results at a mean follow up of 42 months with only one patient having a poor result (Lorentzon et al., 1998). However, in this study periosteal grafting was combined with drilling to allow marrow elements to contribute to the repair process. The benefit of continuous passive motion (CPM) in rehabilitation following surgery is highlighted by Alfredson et al. In their study, 57 patients with patella defects were treated with periosteal grafting alone. Thirty-eight patients had CPM and 19 patients did not. At mean follow-up of 21 months, 76% of patients had good or excellent outcome in the CPM group compared with 53% of patients who had not received CPM. This result was not statistically significant probably as the study was underpowered.

The long term durability of the repair tissue following this procedure is poor. In the patellofemoral joint, Hoikka reported a fair outcome in 4 and good results in 8 patients, four years after surgery (Hoikka et al., 1990). However, twelve years following surgery all patients had poor results. Not much in the way of complications has been reported after this procedure. In the long term, grafts can undergo calcification and this has only been reported in the Chinese literature (Yang et al., 2004).

3.8 Autologous Chondrocyte Implantation

Autologous Chondrocyte Implantation (ACI) as a experimental concept has been around since 1965 (Smith, 1965; Chesterman and Smith, 1968; Bentley and Greer, 1971) although much of the original work was on animal models. Chondrocytes taken from immature rabbits exhibited the potential to divide, whereas chondrocytes from mature rabbits did not (Mankin, 1962a, 1962b, 1963). The ability to expand the number of chondrocytes without losing their chondrogenicity was the next challenge. Chondrocytes were cultured after extracellular matrix enzymatic digestion (Green, 1977) but on cell expansion in vitro, the cells de-differentiated and lost their chondrogenic potential. Chondrocytes did exhibit the ability to regain their chondrogenic potential in agarose gels and by growing the chondrocytes at high density (Benya and Shaffer, 1982; Aston and Bentley, 1982, 1986). Peterson et al. (2002) reported on the ability of autologous or homologous cultured chondrocytes to repair defects in skeletally mature rabbits. Work by Grande et al. (1989) showed that autologous

chondrocytes grown in vitro were responsible for the repair tissue in cartilage defects in rabbits.

The original technique for ACI involved a two-stage procedure where the chondral defect was covered with periosteum harvested from the proximal tibia and sealed with fibrin glue (Brittberg et al., 1994). Although the periosteal patch alone is unlikely to have contributed significantly to the results (Brittberg et al., 1996; Angermann, 1998), growth factors secreted by the periosteum may have stimulated cultured chondrocytes to divide (Minas and Nehrer, 1997; Brittberg et al., 1996). ACI was first used in humans in Sweden in 1994 (Brittberg et al., 1994). The study involved 23 patients with a mean age of 27 years and a mean defect size of 3.1cm^2 up to the subchondral bone but not beyond. Patients with defects in the femoral condyle reported good or excellent results and the biopsy results revealed more hyaline cartilage formation. The results in patella defects were not so encouraging, probably due to the co-existence of additional pathology such as abnormal patella-femoral joint mechanics.

Peterson and Brittberg (2002) reported good or excellent results in 51 out of 61 patients at a mean follow-up of 7.4 years following ACI treatment of isolated femoral condyle or patella chondral defects that ranged from 1.3 to 12cm^2 (Peterson et al., 2002). Compared with these results, Hubbard (1993 and 1996) reported 80% success at 1 year following debridement, but this reduced to 59% at 5 years.

The use of periosteum in ACI procedures (ACI-P) had a number of concerns that became increasingly realised including the requirement of a second surgical procedure at the proximal tibia, the additional damage to healthy cartilage at the time of stitching, low mechanical stability, unequal distribution of the cultured chondrocytes, and reported hypertrophy, delamination and graft failure (Wood et al., 2006). The procedure evolved to use a synthetic type I/III collagen porcine membrane (ACI-C) that showed significantly lower rates of graft hypertrophy requiring secondary surgery than ACI-P (Gooding et al., 2006; Wood et al., 2006; Robertson et al., 2007; Steinwachs and Kreuz, 2007).

3.9 Matrix-Carried Autologous Chondrocyte Implantation

The above concerns led to the development of Matrix-Carried Autologous Chondrocye Implantation (MACI; Verigen, Leverkusen, Germany) that has a similar porcine-derived type I/III collagen membrane (Zheng et al., 2007). The membrane can be secured to the cartilage defect with fibrin glue and does not require additional cover, allowing the procedure to be performed faster and with less extensive exposure (Bartlett et al., 2005). In addition to the brand name MACI, other cell carrier systems are also available on the market. A number of studies were performed to determine the optimum number of cells; Le Baron and Athanasiou (2010) reported that scaffolds with less than 10 million cells/ml resulted in poor cartilage formation. Puelacher et al. (1994) reported that scaffolds with 20-100 million cells/ml resulted in cartilage formation when implanted subcutaneously in nude mice.

A number of studies have shown that MACI and other similar cell carrier systems are as efficacious as the first and second generation ACI techniques (Bartlett et al., 2005; Zeifang et al., 2010) A smaller study by Marlovits et al. (2004) showed complete attachment of MACI grafts to the surrounding cartilage in 14 out of 16 patients by five weeks. One problem in assessing a number of different studies is the use of a number of different scoring systems (Zaslav et al., 2009; Welsch et al., 2010). Ferruzzi et al. (2008) demonstrated superior results with arthroscopic MACI on a hyaluronic acid scaffold compared with ACI-P implanted

in the traditional manner. Although both groups showed statistically-significant increase in IKDC scores up to five 5 years, the MACI group had significantly better scores than ACI-P up to 18 months. In addition, the MACI group had significantly fewer complications and re-operation rates. A longer-term study by Moseley et al. (2010) showed 83.3% 10-year survivorship in 72 patients with the end point being surgery to remove the implanted ACI graft.

There have been a number of studies looking at the post-operative rehabilitation following MACI, and accelerated approaches have shown better outcome compared with traditional rehabilitation (Wondrasch et al., 2009; Ebert et al., 2008).

3.10 The Use of Mesenchymal Stem Cells

ACI and MACI procedures require a sample of tissue taken from articular cartilage to isolate chondrocytes for expansion and re-implantation. Mesenchymal stem cells are a possible alternative cell source for the repair of articular cartilage defects (Khan et al., 2010a; Perera et al., in press). They are available in a number of tissue sources (Mafi et al., 2011; Mohal et al., in press), some that are easily accessible, they increase in number in culture and are mutlipotent with the potential to differentiate down the chondrogenic pathway. Mesenchymal stem cells (MSCs) have been isolated from many tissues including bone marrow (Pittenger et al., 1999), synovial membrane (De Bari et al., 2004), periosteum (De Bari et al., 2006) and articular cartilage (Dowthawaite et al., 2004). Although there have been some studies looking at the potential of these cells to repair cartilage defects in vitro and in animal models (Johnstone et al., 1998; Yoo et al., 1998; Wakitani et al., 1994; Liu et al., 2006, Wilkes et al., 2007, Bonfield et al., 2009) there are few studies in humans.

Autologous culture-expanded iliac crest bone marrow derived mesenchymal stem cells were injected in nine full-thickness patello-femoral articular cartilage defects in three patients. Although the patients reported improved clinical symptoms at final follow-up of 27 months, the histology and MRI did not conclusively show hyaline cartilage repair tissue. In a further study platelet-rich fibrin glue was used as a scaffold to deliver autologous culture-expanded bone marrow mesenchymal stem cells for cartilage repair, similar improved clinical scores were noted at 12 months (Haleem et al., 2010).

Although there is a wealth of literature on bone marrow derived mesenchymal stem cells, these cells may not be the optimal tissue source. Mesenchymal stem cells from bone marrow are difficult to harvest, are low in number and lose their chondrogenic potential in culture (Peltari et al., 2006). Work by others and by us has shown that cells from synovial tissue may be better suited to repair of cartilage defects (Sakaguchi et al., 2005). Work is ongoing to optimise the chondrogenic potential of mesenchymal stem cells using different tissue sources, growth factors (Bosetti et al., 2011; Kanitkar et al., 2011), different culture conditions (Khan et al., 2007), bioreactors (Oragui et al., 2011) and investigating the regulation of their differentiation (Thanabalasundaram et al., in press), their immuno-privileged role (Iyer et al., 2008; Kennard et al., 2011), and their true nature (Khan et al., 2008; Khan et al., 2010b).

4. DISCUSSION

Treating focal articular cartilage damage remains a challenging problem. The short term and to lesser extent mid-term results with bone marrow stimulating techniques such as

microfracture are good and reproducible. The majority of the studied have been case series and there are few randomized controlled trials in the English literature. The most recent RCT compared microfracture (n=33) with ACI (n=34) in patients who had localised OCDs (mean size was 2.4cm^2 in the femoral condyles only. Two years following surgery, ACI patients had similar overall function compared to the microfracture patients (Van Assche et al., 2010). Knutsen had also found no difference in another RCT of ACI versus microfracture in the short- and mid-term period (Knutsen et al., 2004, 2007). Conversely in another RCT, MACI was found to be superior to microfracture at 12 and 24 months following surgery (Basad et al., 2010).

Microfracture is an attractive technique as it can be performed arthroscopically with relative ease in a single satge and is considerable cheaper than cell therapy. In addition, it is not associated with the donor site morbidity of other techniques such as mosaicplasty, perichondrial or periosteal grafting. There is no doubt that microfracture is an effective technique in small well-contained lesions (<2cm^2) but its place in treating larger lesions is yet to be determined.

Horas reported no difference between ACI or mosaicplasty 2 years post-operatively (Horas et al., 2003), whereas Bentley et al. demonstrated superiority of ACI in treating medial femoral condyles a year following surgery (Bentley et al., 2003). Perhaps the place for mosaicplasty is in the treatment of larger lesions (between 2-4cm^2) as cell therapy is not widely available. The National Institute for Health and Clinical Excellence (NICE) has concluded “current evidence suggests that there are no major safety concerns associated with mosaicplasty for knee cartilage defects. There is some evidence for short term efficacy, but long term efficacy is inadequate. In view of the uncertainties about the efficacy of the procedure, it should not be used without special arrangements for consent and audit or research” (NICE 2006).

Regarding whether to perform microfracture or mosaicplasty is largely dependent on surgeon preference and familiarity with the technique. However, athletes have been shown to return to sports activity more quickly after osteochondral autograft transfer than after microfracture treatment (Gudas et al., 2005). Therefore, the American Academy of Orthopaedic Surgeons recommend mosaicplasty for smaller lesions, lesions in high-demand athletes, and lesions with associated bone loss, while microfracture is recommended for medium-size defects with little or no bone loss in lower demand patients.

Other techniques such as the use of carbon fibre rods, perichondrial and periosteal grafting have limited role in cartilage repair due to lack of efficacy and inconsistent results. Although short and medium term results have been encouraging, longer term studies on AMIC are needed before we can define the role for this procedure. Though osteotomy is usually reserved for more widespread degenerative disease that is confined to one compartment in the knee, it can be used adjunctively in cartilage repair if the knee is malaligned (Franceschi et al., 2008).

Overall, none of the non-cell based techniques described have been able to consistently produce durable results and the best form of non-cell based treatment in the long term is still unknown. Long term results from randomised controlled trials are needed to answer these questions though this has always been difficult to conduct in orthopaedics. Current NICE recommendations are to enroll all patients receiving ACI into new or ongoing clinical studies (NICE, 2005), and although currently there are no long term reports on cell based therapies, this should change in the coming years. Although the results with mesenchymal stem cells

have been promising, many hurdles still need to be overcome (Khan et al., 2009; Mahapatra and Khan, 2011), and it is likely that ACI and MACI will remain the standard of care for larger full thickness chondral defects in the knee for the next few years.

5. CONCLUSION

Focal articular cartilage defects are challenging clinical problems that progress to more generalised lesions. Only cartilage injuries that extend to the subchondral level show some capacity for repair due to the release of bone marrow derived mesenchymal stem cells. Bone marrow stimulating techniques such as microfracture are effective in small well-contained lesions (<2cm^2) and have the advantages of being performed arthroscopically as a single stage and cheaper costs compared to cell-based therapies. Mosaicplasty, carbon fibre rods, and perichondrial or periosteal grafting are associated with donor site morbidity. The best form of non-cell-based treatment for focal articular cartilage defects in the long term is still unknown. Longer term studies on AMIC may help define the role for this procedure. ACI and MACI are currently used in clinical practice to treat larger full thickness chondral defects in the knee. There are a small number of studies using mesenchymal stem cells MSCs and further in vitro and in vivo studies are needed before this treatment is optimised.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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