

Current strategies for knee cartilage repair

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SUMMARY

Defects in knee articular cartilage (AC) can cause pain and disability and present the clinician with an extremely challenging clinical situation. This article describes the most up-to-date surgical techniques that aim to repair and/or regenerate symptomatic focal defects in AC, which include arthroscopic debridement, microfracture bone marrow stimulation and autologous osteochondral allografting, with an emphasis on autologous chondrocyte implantation. In the future, refinement of tissue-engineering approaches promises to further improve outcome for these patients.

Key points

- Articular cartilage defects are a common injury, particularly in the young and active.
- They still present a challenging problem with no universally accepted treatment.
- Whether to treat must be directed primarily by clinical information, not solely by the presence of a lesion.
- Microfracture is a successful temporary repair procedure, recommended for small lesions, which produces fibrous tissue and can provide relief for several years.
- Autologous chondrocyte implantation offers the possibility of regeneration with a hyaline tissue and is the recommended front-line treatment for larger defects.
- Future research will refine tissue-engineering techniques to improve outcome with cell-scaffold treatments.

Review Criteria

Articles published in English were identified by searching PubMed in December 2009 using the following search terms: 'cartilage and repair', 'cartilage and regeneration', 'cartilage and articular chondrocyte implantation', 'cartilage and osteochondral autograft', 'cartilage and microfracture' and 'cartilage and periosteal transplantation'.

Introduction

Knee articular cartilage (AC) defects have long presented a challenge to physicians. In 1743, the famous English anatomist William Hunter wrote 'an ulcerated cartilage is a trouble-some problem... that, once destroyed, it is not recovered' (Figure 1) (1). Today, more than 250 years later, cartilage damage is still an issue for physicians and patients, and there is still no universally accepted and successful treatment approach for damaged AC. However, the result of research into novel surgical therapies developed over the last two decades, described in this article, has the potential to consign this statement to history.

Importance of knee cartilage defects

Articular cartilage lesions are common. In patients undergoing arthroscopic investigation for knee symp-

toms, the incidence of cartilage defects has been found to be 61% (2) and 63% (3), and the prevalence of work- or sport-related articular lesions has been reported at 22% and 50% (4,5). Furthermore, in patients with anterior cruciate laxity, the incidence of articular pathology is as high as 54% (6). Although more common with age, these injuries are also frequent in patients < 55 years old (3,7), in whom a prosthetic joint replacement, with a limited lifespan, is not recommended. Therefore, alternative treatments are required. Focal AC defects are most often traumatic in origin, resulting from a high-load impact or repetitive shear and torsional loads on the superficial zone of AC (8). A small proportion of lesions are caused by osteochondritis dessicans (< 5%) (9). Focal AC defects are separate from osteoarthritis, a chronic degenerative disease, which has distinct clinical, radiological and arthroscopic findings.

Natural history of knee cartilage defects

Hyaline AC is predominantly composed of a unique extra-cellular matrix (ECM), formed from embryonic mesenchyme in a complex and incompletely understood developmental process (10). The two principal components of AC are proteoglycans – negatively charged glycosaminoglycan chains that swell and hydrate AC – and collagen type II – a fibrillar collagen that traps the proteoglycans and provides tensile strength. This ECM is specialised to cope with its singular biomechanical environment; to regain a functional joint, cartilage defects would ideally be replaced by tissue of this precise composition.

Injury to some musculoskeletal tissues, such as bone, results in recapitulation of embryonic development processes and regeneration of fully functional tissue identical to the pre-injured tissue. However, there are several barriers to intrinsic AC repair: (i) it is avascular, meaning that the nutrients required for energetic repair processes and the removal of metabolic waste products are limited by diffusion to/from surrounding tissues. (ii) It is relatively acellular; therefore few cells are available to affect repair. These obstacles conspire to limit repair of defects to a fibrocartilaginous substitute tissue with different molecular composition (more type I collagen, less proteoglycan) and biomechanical behaviour (less proteoglycan and collagen type II, more collagen type I), compared with the original hyaline tissue (11,12).

Despite this clear pathological response to injury, the natural history of untreated AC lesions is not fully understood (13). Shelbourne et al. reported a series of patients identified with AC defects discovered at the time of arthroscopic cruciate ligament reconstruction. Patients left with untreated AC lesions had similar subjective patient scores at an average follow up of 9 years than control subjects with no AC defects. Interestingly, the authors also

noted that a number of patients with significant AC defects have no/mild clinical symptoms (5). In another treatment, intervention trial patients treated only with debridement and no surgical repair procedure showed spontaneous improvement (14). Therefore, although some lesions will be asymptomatic, AC defects have the potential to manifest as continued joint pain, impaired movement and functional disability that will need treating in a carefully selected group of patients. Additionally, it is known that AC defects increase the risk of osteoarthritis, which may require knee replacement (15). Therefore, it is desirable to intervene not only to reduce current morbidity but also to reduce the likelihood of future joint disorder.

Patient selection and indication for surgery

A wide-range of non-specific symptoms may lead clinicians to consider that an AC defect is the source of a patient's pain, including locking, pain at rest, swelling, pain with activity, instability and retropatellar crepitus (16,17). Approximately, two-thirds of patients with chondral defects have associated ligamentous or meniscal pathology, and AC damage has been reported in association with 23% of anterior cruciate ligament (ACL) injuries and 54% of knees with chronic ACL laxity or instability (6). Focal AC defects are distinct from osteoarthritis, which often involves more widespread cartilage damage and prominent subchondral bony changes, is predominantly a disease of old age and has a chronic, gradually worsening course.

Cartilage lesions are graded I–IV according to the International Cartilage Repair Society (ICRS) scale (18). Grade I lesions are nearly normal with only superficial fissures, grade II lesions extend < 50% of cartilage depth, grade III are severely abnormal lesions extending more than 50% of cartilage depth,

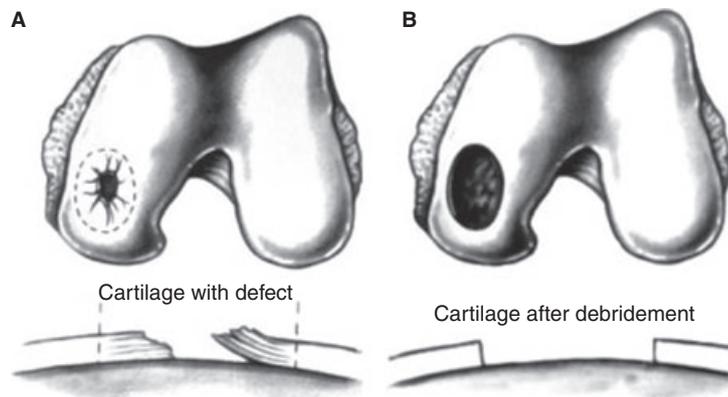


Figure 1 Schematic of a focal knee cartilage defect. (A) A fibrillated cartilage lesion. (B) Debridement of the defect to healthy cartilage with smooth vertical borders. Reproduced with permission from (72)

but not into the subchondral bone and grade IV lesions include the subchondral bone.

Clinical examination is supported by arthroscopic assessment, the gold standard investigation for chondral defects, which allows direct visualisation of the chondral surface. In addition, magnetic resonance imaging (MRI) has a high sensitivity and specificity to detect chondral defects [$> 95\%$ for grade III lesions (19)]. High resolution MRI can provide sufficient information for operative planning and might in future obviate the need for diagnostic arthroscopy. Most importantly, the commonly occurring asymptomatic AC defect makes it essential that care is taken during clinical examination and investigations to determine that findings correlate with clinical symptoms, therefore ensuring that treatment is not misdirected (5). Patient selection and indications for surgery vary according to the treatment type and are considered further below.

Current treatment options

Orthopaedic surgeons have developed a wide arsenal of treatment options for treating focal knee AC defects (20). Those most commonly employed today include, but are not limited to: (i) arthroscopic debridement, in which loose cartilage is trimmed, (ii) microfracture, in which bone marrow based repair is stimulated, (iii) autologous osteochondral grafting, in which bone-cartilage plugs are harvested from non-weight bearing joint sites and implanted directly into the defect and (iv) autologous chondrocyte implantation (ACI), a two-stage procedure involving harvest of chondrocytes, growth *in vitro*, then re-implantation.

Which treatment is chosen depends on several factors, including size of lesion, availability of particular treatments and the age and requirements of the patient. Small lesions may be conservatively managed with arthroscopic debridement and careful monitoring (14,21), whereas more extensive lesions require

greater intervention. The first choice treatment for lesions $< 2.5 \text{ cm}^2$ is bone marrow stimulation by microfracture (8,22–24). Larger lesions may be treated by mosaicplasty (17); this technique is limited by the availability of donor tissue, or by autologous chondrocyte transplantation, which is becoming more widely available (8). Other treatments, such as abrasion chondroplasty and the use of carbon fibre pads, are either less widely practised, or have been superseded and are therefore not discussed.

Arthroscopic debridement

Small defects in which there are loose, overhanging flaps of cartilage may initially be treated by arthroscopic debridement (14,21). These lesions often present with locking. However, larger, more complex defects, perhaps with no obvious loose body, require more complex procedures, which either stimulate repair tissue (microfracture) or replace damaged cartilage (osteochondral transplantation or ACI).

Bone marrow stimulation by microfracture

Bone marrow stimulation by microfracture is widely considered the first choice treatment for small lesions ($< 2.5 \text{ cm}^2$) (8,22–24) (Figure 2). Bone marrow stimulation techniques aim to induce bleeding for the subchondral bone followed by the formation of a fibrin clot, migration and recruitment of bone marrow derived stem cells and the formation of a fibrocartilaginous repair tissue that covers full-thickness chondral lesions. Bony drilling into the defect, first described by Pridie in 1959 (25), was prevalent until the advent of microfracture in the 1990s (26). Pridie drilling uses a hand-driven or motorised drill to penetrate the subchondral plate. This is thought to cause heat-related tissue damage, whereas microfracture uses a gentler arthroscopic awl, which does not generate significant heat (27,28). Microfracture is now more popular than other bone marrow stimulation techniques [drilling and arthroscopic abrasion arthroplasty (29)].

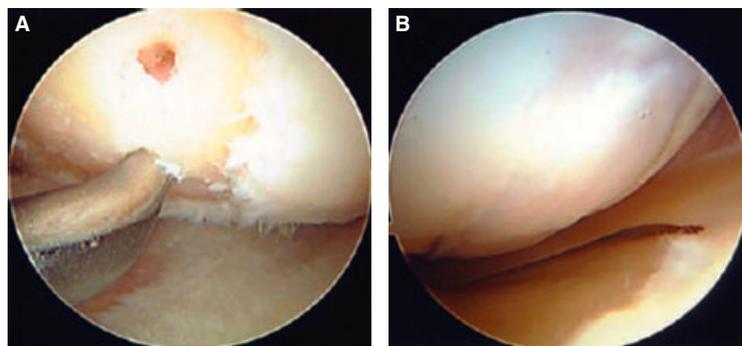


Figure 2 Bone marrow stimulation by microfracture. (A) Small holes 3–4 mm apart are created in the bone of the defect. Bleeding is induced, which results in healing by production of fibrocartilagenous tissue. (B) Femoral condyle defect that has been filled with newly formed fibrocartilagenous tissue. Reproduced with permission from Lutzner et al. (73)

Microfracture has demonstrated good or excellent results in 60–80% of patients (27,30,31). There is some evidence that MF works best in patients under 40 years old that might have intrinsically superior healing responses to those in older patients (32). It benefits from the low-morbidity of an arthroscopic procedure with a relatively quick recovery period and low complication rate (30,33).

Treatable lesions are 1–2.5 cm² large and well shouldered with protected edges (8). Microfracture involves debridement of unstable cartilage to bone level to form a stable rim of healthy cartilage around the defect. Specially designed awls are then used to make multiple holes 2–4 mm deep and 3–4 mm apart in the subchondral bone (34). Rehabilitation includes continuous passive motion and partial weight bearing for 6–8 weeks. Interestingly, non-human primate models of microfracture show repair tissue to be immature after 6 weeks, suggesting a longer rehabilitation period might be necessary (35).

The procedure may be less-well suited to the patello-femoral joint or the tibia, which in one study showed deterioration after 18 months following microfracture (24), or to lesions larger than 4 cm², which have been reported to fair better after treatment with autologous chondrocyte transplantation (22,23). Complications include degenerative changes in the subchondral area, such as cysts, osseous overgrowth and intra-lesional osteophytes in approximately 33% of patients (24,27). The significance of these findings has not been proven, but changes to the subchondral plate likely underlie failed MF treatment (33).

Microfracture is not a curative treatment, but it can provide relief for a number of years. However, doubts remain over the durability of the repair tissue produced, which is fibrocartilagenous and has inferior biomechanical properties compared with hyaline tissue. Mithoefer et al. conducted a systematic review examining the clinical efficacy of MF for knee AC defects. They identified six randomised control trails (RCT), which all showed improved knee function during the first 24 months post-operation, but the longevity of the initial improvement was not consistent between studies (36). Furthermore, a recent report of microfracture used to treat professional athletes concluded that ‘from a strict scientific stand point an untreated control group would be valuable to demonstrate that microfracture does not just mirror the natural course of healing’ (37). There are currently no published studies comparing MF (or any other intervention) to an untreated control group. This should be an important future research goal.

Autologous osteochondral grafting/mosaicplasty

Autologous osteochondral allografting, also known as mosaicplasty, most commonly involves transplantation of small (< 1 cm²) cylindrical cartilage plugs harvested from non-weight bearing areas such as the lateral femoral condyle or the trochlea, directly into the defect in a one-stage procedure (17) (Figure 3). The use of different size plugs allows defect filling of more than 90%, and the graft needs to be perpendicular and flush to the surface to prevent catching with knee motion (17). This technique has the advantage of directly implanting hyaline cartilage onto the defect. The procedure may be carried out open or arthroscopically and is not recommended in

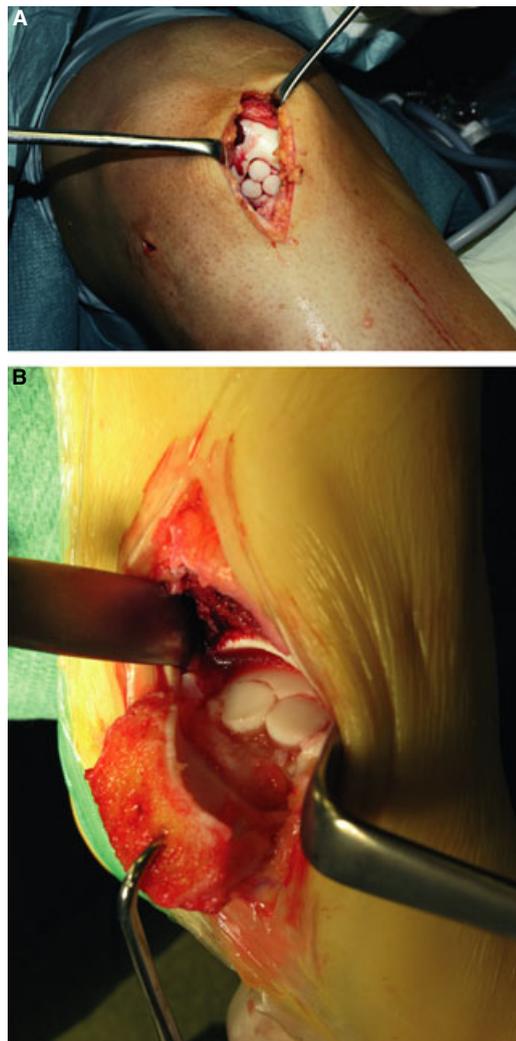


Figure 3 Arthroscopy mosaicplasty. (A) Miniarthrotomy mosaicplasty on the medial femoral condyle for the treatment of a chondral defect. Three osteochondral plugs can be seen implanted in the defect. (B) Mosaicplasty on the medial talar dome to treat an osteochondritis dessicans defect. Images kindly provided by Laszlo Hangody

individuals over 50 years old (17). Good to excellent results have been reported in 85–95% of treated defects of the femoral condyles, tibial surfaces and patellar/trochlear lesions (38–43).

It is important to note that repair using autologous tissue technique is most suited to small (< 4 cm²) lesions, being limited by the availability of donor tissue and by potential donor-site morbidity (17,44). Larger defects may be filled with allogeneous cartilage tissue from a cadaveric donor, although this risks immunologic rejection and disease transmission from donor to recipient. Therefore, osteochondral allografts are generally reserved for uncontained (not well-defined) lesions > 4 cm² where there is significant osseous damage (8).

Autologous chondrocyte implantation

By 2003, more than 15,000 patients have undergone ACI worldwide (45), and it is now widely considered the frontline treatment for defects larger than 2 cm² (8) (Figure 4). The procedure is recommended for ICRS grade III/IV lesions of the femoral condyle or trochlear region, but more recently has been used with success for patellar lesions. The optimum candidate is a highly motivated patient, < 50–55 years old, with a high functional demand and high potential for compliance with the long-term rehabilitation required [reviewed in (8)].

Indications

The size of a lesion best suited to ACI is still debated. Conventional thinking is that lesions

< 2–2.5 cm² may be treated initially with microfracture and that ACI may be used in patients that continue to have pain after microfracture. However, although microfracture was considered a ‘non-bridge-burning procedure’ (33), a recent study suggests that previous microfracture reduces the chances of successful ACI by 30% (33). Bone involvement is not a contraindication, but when bone involvement is deeper than 6–8 mm, autologous bone grafting should be undertaken (46). Reciprocal (kissing) lesions are generally a contraindication.

Pre-operative assessment

In pre-operative planning, weight loss is central, and a body mass index < 30 kg/m² is recommended. Weight loss has been associated with improved activities of daily living scores and SF-36 Physical Component Summary Scores following cartilage repair procedures (27). Clinical assessment should include knee alignment and associated injuries. Malalignment should be corrected by osteotomy, and knee ligaments reconstructed. Meniscal lesions require repair or resection at initial arthroscopy. Radiographic assessment includes postero-anterior weight bearing views to assess for medial/lateral compartment narrowing, bilateral Merchant views to assess patellar facet wear, subluxation and tilt, and bilateral long-limb standing radiographs to examine the leg axis and potential sites of increased load to the repair site. MRI has a high sensitivity and specificity (over 90%) for detecting AC defects, but only lesions that correlate with clinical symptoms should be treated.

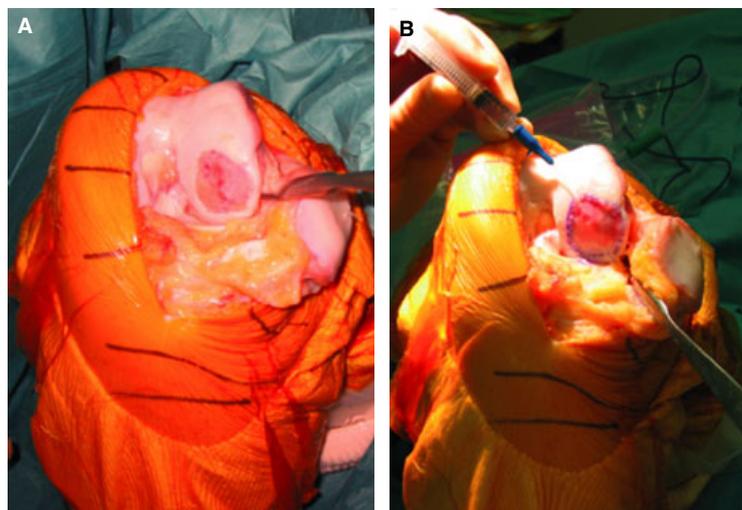


Figure 4 Autologous chondrocyte implantation. (A) A focal cartilage defect that has been debrided to healthy cartilage. (B) Autologous cultured chondrocytes have been implanted into the defect, over which a periosteal flap will be sutured. Reproduced with permission from Gikas et al. (48)

Surgical technique

Two separate procedures are required for ACI. First, arthroscopic assessment is performed after physical examination and radiographic studies. If areas of ICRS grade III/IV are found, the lesions are measured. If the reciprocal surface is not severely damaged and the patient is an appropriate candidate for chondrocyte implantation, a biopsy is taken. Harvest is from a non-weight bearing area of AC, such as the medial edge of the trochlear groove. Approximately, 200–300 mg of tissue are taken, which corresponds to approximately 300,000 cells. It is important to remove tissue from a healthy area in order that 'normal' chondrocytes are collected. Chondrocytes are cultured for 4–6 weeks in a laboratory compliant with Good Manufacturing Practice guidelines. It is important that chondrocytes are not cultured longer than this, or phenotypic changes emerge. Either a chondrocyte suspension or chondrocytes seeded on a collagen-based scaffold [matrix-assisted autologous chondrocyte implantation (MACI)] are then implanted in a second procedure. The defect is prepared by debriding the edges to normal AC. Damage to the underlying chondral bone is avoided to prevent bleeding into the defect. In ACI, a periosteal graft, which may be harvested from the proximal tibia, is used to cover the implanted cells (47), or chondrocytes can be implanted beneath a collagen membrane (ACI-C). In the MACI technique, cells are seeded on a collagen type I/III scaffold at a precise concentration (1 million cells per cm²). The membrane is placed directly into the defect and secured with fibrin glue, eliminating the need for suturing to surrounding cartilage and use of a cover, which can damage surrounding healthy cartilage.

Rehabilitation

Rehabilitation protocols vary widely, but always involve a long and cautious process, requiring high motivation and patient compliance. When planning rehabilitation, it is important to remember that a biological healing process is occurring, which involves cell proliferation (0–6 weeks), matrix production (first 6 months) and matrix remodelling (6 months onward). Most protocols require reduced weight bearing for 10 weeks, aiming to avoid impact loading and twisting or shearing forces, which might damage the repair tissue. One protocol uses a plaster of Paris for week one, then toe-touch weight bearing with flexion-extension exercises at weeks 2–6 (48). From 6 weeks, partial weight bearing is used, and from 10 weeks, full weight bearing is allowed. Other regimes use passive movement from day one

onwards, which aims to stimulate implanted cells via mechanical signals as early as possible (49). It ought to be noted that the ideal mobilisation protocol aims to optimise the repair process, and it is tailored to the individual case. Well-contained lesions are protected by surrounding cartilage and may begin weight bearing at 4 weeks, whereas large poorly contained lesions should not bear weight fully until 8–12 weeks postsurgery (8).

Post-operative assessment

Arthroscopy remains the gold standard for post-operative evaluation, often carried out at 1 year post-operation, and allows visualisation of the repair and biopsy for histological assessment. Probe indentation stiffness can also be measured and has demonstrated up to 80% stiffness compared with native AC (50). Gikas et al. demonstrated progressive development from fibrocartilage to hyaline cartilage with increasing time from operation in patients having undergone ACI/MACI. The appearances of the repair tissue can also be investigated with MRI (51). In one series, ACI provided better defect filling than microfracture (52). More sophisticated MRI techniques use intravenously administered gadolinium, which can penetrate cartilage, and T1 imaging can estimate glycosaminoglycan content and T2 mapping allows evaluation of collagen content [for review see (53)].

Clinical results of ACI

Clinical results for ACI have been encouraging. Numerous case-series report positive effectiveness of ACI for treatment of knee AC defects, with follow up now available for more than 10 years postprocedure (54–57). Furthermore, there are RCT comparing ACI with microfracture (20,23,58) and to mosaicplasty (58), and these RCTs have been reviewed in an attempt to determine an optimum treatment for focal AC defects.

A Cochrane Collaboration meta analysis identified four RCT comparing ACI with microfracture or mosaicplasty that met their eligibility criteria (23,59–62). One of these trials reported superior outcome for ACI vs. mosaicplasty (59), while the other trials did not find a superior treatment. In one study, 1 year after treatment, ACI was associated with a tissue regenerate that was superior to that of microfracture (23). Overall, they could not find evidence to support ACI over microfracture or mosaicplasty, and concluded that further RCT are required.

Since publication of the Cochrane review (2006) (62), further RCTs have been published. Knutsen et al. reported no difference in clinical or radio-

graphic outcome measures at 5-year follow up of patients treated with either microfracture or ACI (20). Saris et al. report that similar short-term clinical outcome was for ACI and microfracture groups (63). Similarly, Van Assche et al. reported on 67 patients randomised to microfracture or ACI. Follow up at 2 years did not show differences in functional outcome (64).

Recently, Magnussen et al. reviewed five RCT comparing ACI/MACI, osteochondral autograft transfer and microfracture. All treatments improved clinical outcome measures compared with pre-operative assessment, but no technique consistently had superior results and no study used non-operative control groups (65). The authors' recommendation is that a large prospective trial be conducted and that non-operated controls be included.

These trials are consistent in reporting clinical improvement following ACI. Furthermore, economic analysis has demonstrated cost effectiveness of ACI (66). There is emerging evidence that the repair tissue produced in ACI is more hyaline-like and more durable than that following microfracture (20,63). However, there is currently no firm evidence that ACI provides improved patient outcomes compared with either microfracture or mosaicplasty. Furthermore, the quality of trial methodology investigating knee AC defects could be improved by adequately describing randomisation procedures, including untreated control groups, use of validated outcome measures and the use of an independent investigator or outcome assessment (62,67).

Matrix-assisted/induced autologous chondrocyte implantation

Autologous chondrocyte implantation is considered to be the first widely available and commercially successful cell-based therapeutic intervention. Undoubtedly, in the future, more cellular therapies will become available to treat a wide variety of disorders. The pioneering position of ACI at the forefront of medical technology has understandably led to close scrutiny from medical regulatory authorities. Wood et al. reported that the rate of adverse reactions in patients treated with Carticel, an autologous chondrocyte implant system, was 3.8% (497/7500). Adverse reactions included graft failure (25%), delamination (22%) and tissue hypertrophy (18%) (68) and most often occurs within 6 months after surgery in approximately 25% patients and can require surgery (55).

It is thought that tissue hypertrophy is related to the use of a periosteal graft to cover the implanted chondrocytes, which in addition is technically diffi-

cult to harvest and can cause joint stiffness and arthrofibrosis. The technical advantages of scaffold-based techniques (e.g., MACI), which remove the need for an arthrotomy and the risk of periosteal hypertrophy, have led to some surgeons preferring scaffold techniques (55). Therefore, there has been evolution towards implants in which cells are seeded in a 3D matrix that does not require periosteal cover. Since the late 1990s, when the European Drug Agency licensed the use of collagen and hyaluronan based scaffolds for implantation with cultured autologous chondrocytes, several different matrix-based implants have been devised, including MACI (Verigen Transplantation Service, Copenhagen, Denmark), Hyalograft C (Fidia Advanced Biopolymers Laboratories, Padova, Italy) and CaReS (Ars Arthro, Esslingen, Germany). Mid-long term follow up is now becoming available (69) and suggests that MACI gives similar or slightly improved clinical outcome compared with ACI (48) or microfracture (57). Biopsy results have also been encouraging, showing the production of hyaline cartilage (48,51). Nevertheless, RCT are required to investigate these new procedures (70).

Histological analysis of repair tissue following ACI/MACI reveals that approximately 50% of patients have hyaline-like or mixed hyaline and fibrocartilage tissue (20,51). Although this is certainly improved compared with microfracture (63), why some chondrocyte implants produce hyaline tissue and others fibrocartilaginous tissue is not known. This may be because of specific patient, cell-culture or knee injury factors, and investigation into predicting which patients respond best will be important in the future. Saris et al. have begun to investigate manipulation of histological outcome by characterising and selecting chondrocytes for implantation by gene expression profile analysis for a number of cartilage marker genes, such as collagen type II. They found that superior structural tissue was formed in the ACI group, which used characterised chondrocytes, compared with microfracture. This is a promising approach, but further study comparing un-characterised cultured chondrocytes is required to determine whether cell-selection results in improved histological outcome (63).

Future perspectives

Treatment for AC lesions has pioneered tissue-engineering techniques, illuminating a path that other therapeutic interventions will undoubtedly tread. Improvement in clinical outcome has been demonstrated following ACI treatment, and there are clear routes forward which involve the development of matrix-based implants. Currently, minimally invasive

procedures such as microfracture are probably best for small defects (< 2.5 cm²), and ACI for larger lesions. However, it has been said that no treatment has demonstrated long-term efficacy (16,68). The evidence for ACI providing superior outcomes compared with treatment by microfracture bone marrow stimulation is not yet well established (62,67), and improvement in the quality of RCT that are undertaken is required (62,67).

Chondrocyte implantation holds great promise for future development. The refinement of tissue-engineering techniques will include evaluation of different cell-scaffold combinations, genetic manipulation of implanted cells and use of alternative cell sources such as mesenchymal stem cells. In the future, therapies might incorporate mechanical stimulation of the tissue *ex vivo* prior to implantation (NeoCart; Histogenics, Waltham, MA, USA), the use of allogenic chondrocyte transplantation (DeNovo ET), use hydrogel or hyaluronic acid-based scaffolds (71). There is also a push to develop single-stage arthroscopic cell-based treatments that use allogeneous cells, or autologous cells of non-cartilage origin (e.g., mesenchymal stem cells) cultured and differentiated *in vitro* prior to implantation. Although none of these procedures yet has regulatory approval, the scope for future development of chondrocyte implantation techniques will, hopefully, result in superior treatments.

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