Cartilage transplantation

Chondral injuries are common sequelae following musculoskeletal trauma. This article reviews different techniques of cartilage regeneration undertaken in the past, and focuses on the recent advances in the field of tissue engineering.

Articular cartilage covers the articular ends of bones in synovial joints. In large human joints such as the hip and knee, cartilage has a thickness of 2–4 mm. The principal function of articular cartilage is to bear load through a range of motion during functional activities.

Cartilage consists of an abundant extracelluar matrix and a small number of cells. Extracelluar matrix is principally composed of water (approximately 75% of weight) collagen and proteoglycan. Collagen is the body's most abundant protein and is formed from alpha and beta helices. Proteoglycan is composed of proteins and di-saccharides formed from keratin sulphate, chondritin sulphate and hyaluronic acid. The cells in cartilage are known as chondrocytes. Cartilage is devoid of nerves and blood vessels.

The functional organization unit in articular cartilage consists of the following zones: superficial zone, mid zone, deep zone, tidemark, calcified zone and subchondral bone (*Figure 1*).

Injuries to the articular cartilage

Chondral injuries are common sequelae following musculoskeletal trauma. Chondral injuries involve damage to the articular cartilage while osteochondral injuries involve damage to the articular cartilage and the underlying bone. The natural history of articular cartilage lesions is poorly understood. The most accepted method of describing cartilage degeneration is the Outerbridge classification (Outerbridge, 1961) (*Figure 2*). The depth of the defect is critical in determining the repair response (Johansen, 2004). First, partial thickness chondral defects do not repair spontaneously, because the chondrocytes in a differentiated cartilage (in superficial and mid zone) have little intrinsic potential for replication (Mankin, 1982). Second, the chondrocytes are embedded in a tough extracellular matrix and cannot migrate to the area of damage like other epithelial tissues.

In contrast, full thickness chondral defects penetrate the underlying subchondral bone by extending beyond the 'tidemark' allowing migration of the bone marrow mesenchymal stem cells to the damaged area. This intrinsic repair response produces fibrocartilage. Fibrocartilage has diminished resilience and poor wear characteristics as compared to hyaline cartilage, predisposing the early onset of osteoarthritis (Mankin, 1982).

Figure 1. Section through the cartilage showing normal anatomy.

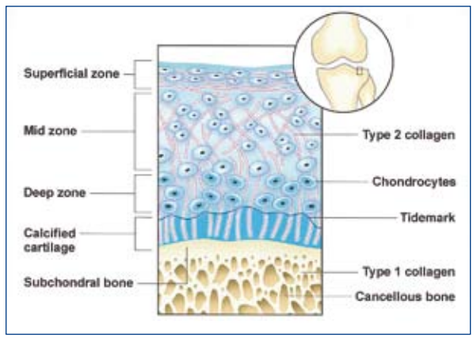
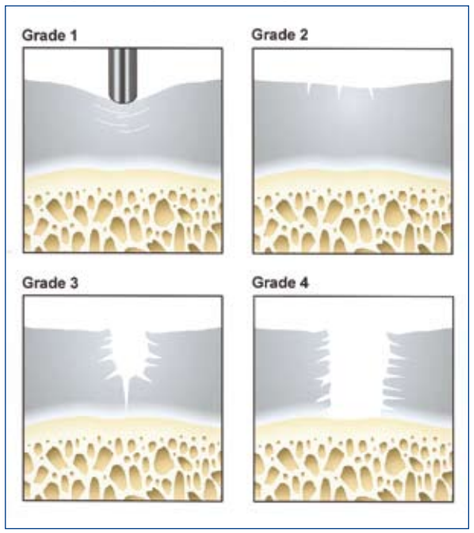


Figure 2. Outerbridge classification (modified): grade 1 softening and swelling; grade 2 fragmentation and fissuring; grade 3 partial loss of cartilage; grade 4 complete loss of cartilage to bone.



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Cartilage repair: surgical interventions

Since the load-bearing function of articular cartilage largely depends on the quality of the extracellular matrix, regenerating repair tissue with the same functional and mechanical properties of hyaline articular cartilage is the major challenge to orthopaedic surgeons and tissue engineers.

The surgical interventions aimed at regenerating articular cartilage can be broadly divided into three types as outlined below.

Mesenchymal stem cell stimulation techniques

Many arthroscopic repair strategies (debridement, drilling and microfracture) utilize the intrinsic repair response to induce the formation of repair tissue within the defect; the cartilage formed is fibrocartilage. Debridement (abrasion), microfracture and drilling are also known as marrow stimulation techniques.

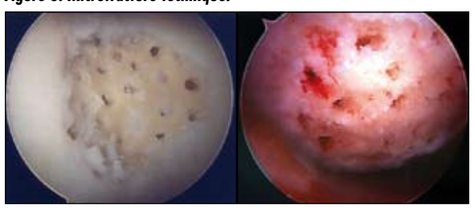
Debridement

This involves meticulous removal of all unstable cartilage and abrasion of the calcified layer to allow new tissue to form in the base. Hubbard (1996) studied the results of debridement on symptomatic knees with Outerbridge grade 3 or 4 well-contained defects on the medial femoral condyle. Results of this procedure were initially excellent and only gradually deteriorated over a 5-year period, at which time 65% of patients were pain-free (Hubbard, 1996).

Microfracture

This is a modification of the Pridie drilling technique (Pridie, 1959) and consists of accurate debridement of all unstable and damaged articular cartilage down to the subchondral bone plate, while maintaining a stable perpendicular edge of healthy cartilage (*Figure 3*). The microfracture procedure was introduced by Steadman et al (Steadman et al, 1997; Miller et al, 2004). An arthroscopic awl is used to make multiple holes in the defect 3–4 mm apart. As a result, the defect is filled with a so-called super clot, which is considered to be an optimal environment for mesenchymal marrow stem cells to differentiate into stable tissue (Sledge, 2001). Early joint rehabilitation with continuous passive motion and protected weight-bearing for 6 weeks is important for its success.

Figure 3. Microfracture technique.



Microfracture has certain advantages over drilling which include reduced thermal damage to subchondral bone and the creation of a rougher surface to which repair tissue might adhere more easily. It is also easier to penetrate a defect perpendicularly with a curved awl during an arthroscopic procedure as compared with a drill. There are currently no published studies which compare microfracture with drilling, or debridement.

The ideal candidate for a microfracture procedure is a patient with a full thickness chondral defect less than 4 cm in a weight-bearing surface of a well-aligned and stable knee (Johansen, 2004). Patients with inflammatory arthritis, elderly (>65 years) and those not motivated for rigorous physiotherapy are poor candidates for microfracture.

Substitution replacement techniques

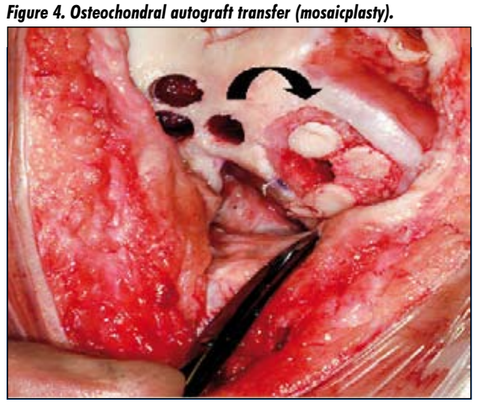
Substitution replacement techniques use allografts and autografts (osteochondral autologous transplantation (OATs) and osteochondral allografts) to fill the defect with articular cartilage.

Osteochondral autologous transplantation

Osteochondral autograft transfer was first described in 1993 (Matsusue et al, 1993). In this procedure, osteochondral plugs are taken with a cylindrical cutting device and used to fill an articular cartilage defect. Plugs are usually harvested from low weight-bearing areas of the trochlea or the femoral condyle and introduced as a mosaic to fill the defect (*Figure 4*). The technique is usually undertaken as an open procedure, although it is possible to perform it arthroscopically (Huang et al, 2002).

The advantages of this technique are that defects can be filled immediately with mature, hyaline articular cartilage and that both chondral and osteochondral defects can be treated in the same way. However, this technique is associated with an extensive margin of cell death that is likely to compromise lateral integration and articular reconstruction. Also, cell survival in the

Figure 4. Osteochondral autograft transfer (mosaicplasty).



transplanted cartilage appears to reduce with time. Donor site morbidity is always a concern. Bentley et al (2003) advised against using mosaicplasty on the patella.

Hangody and Fules (2003) recommend that defect size should be limited to smaller lesions of between 1 and 4 cm^2.

Perichondral grafts

Homminga et al (1990) used autologous strips of perichondrium and fixed them to the subchondral bone with fibrin glue. Long-term results of 88 patients with a mean follow-up of 52 months showed good results in only 38%. This technique is therefore no longer in use.

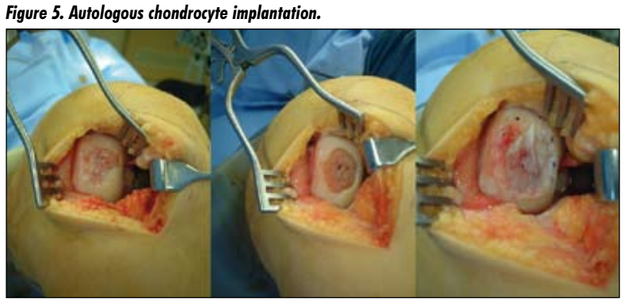
Carbon fibre implants

Fine spaces between the fibres of carbon fibre rods direct the regeneration of tissues on to the surface of a joint. Another use of carbon fibre is as a mesh to support ingrowth of new bone and fibrocartilage. Good clinical results have been reported in both chondral and osteochondral defects (Nicholson et al, 1998). Carbon fibre matrix is more commonly used in the patella, but reports by Meister et al (1998) revealed good results in only 41% of patients. The main disadvantage of carbon rods is the introduction of non-absorbable material deep in the subchondral bone. In early osteoarthritis, Brittberg et al (1994a) had an 83% success rate in 37 patients studied prospectively.

Osteochondral allografts

These are derived from cadaver donors, and have been used to treat osteochondral defects with varying degrees of success. It has been demonstrated experimentally that fresh tissue is more successful than frozen tissue in terms of cell death and mechanical stability. Despite the immunologically privileged position of articular cartilage, an immune response is still a potential problem with this approach. This technique has been widely used with functional and symptomatic joint improvement. While allogenic osteochondral transplantation has been shown to benefit large osteochondral defects, the potential of disease transmission and a high rate of rejection are responsible for its limited use in recent times.

Figure 5. Autologous chondrocyte implantation.



Cell or biological replacement options

Cell-based replacement methods currently involve the transplantation of in-vitro expanded autologous chondrocytes into the defects to form repair tissue. Current research in tissue engineering is focused on exploring the potential use of mesenchymal stem cells as a source for cartilage regeneration, as well as the combination of cells with biodegradable scaffolds.

Autologous chondrocyte implantation

The technique of autologous chondrocyte implantation (ACI) was first introduced successfully in humans by Peterson et al in Gothenburg in 1994 and was the first application of cell engineering in orthopaedic surgery (Brittberg et al, 1994b). ACI is a two-stage procedure (*Figure 5*). During the first stage, an arthroscopy of the knee is performed to harvest a piece of full thickness cartilage from a low weight-bearing area of the femoral condyle. The cartilage cells are then grown and expanded in vitro over a period of 3–4 weeks. In the second stage operation, the knee joint is opened and the culture-expanded autologous chondrocytes are injected into the chondral defect underneath a biological membrane patch, for example, periosteum from the proximal medial surface of the tibia, or a manufactured membrane called Chondro-Gide (Geistlich Biomaterials, Wolhusen, Switzerland).

Peterson and colleagues published the results of 23 patients with a mean follow up of 39 months (Brittberg et al, 1994b). They reported good or excellent clinical results in 70% of cases (88% of femoral condylar defects) and the neo-cartilage showed hyaline-like cartilage. A more recent publication from this group has shown durable results in patients up to 11 years post-operation, and good results following treatment of osteochondral lesions (Peterson et al, 2002). In the studies where histological analysis has been performed it is apparent that in some specimens ACI is capable of producing tissue that is hyaline-like. However, the best repair tissue is not morphologically or histochemically identical to normal hyaline cartilage, and fibrocartilage is found in a high proportion of samples. The results from these small studies suggest that symptoms improve in over 80% of patients and 98% of those with good results at 2 years continue to have good results 9 years after surgery. Patellar defects are associated with poorer results compared to femoral and tibial defects.

Knutsen et al (2004) conducted a randomized trial of ACI *vs* microfracture in Norway. With four patients in each group, postoperative results at 2 years showed little difference between treatments, with both groups showing significant clinical improvements, and the microfracture group doing slightly better on the physical component of the Short-Form-36, a widely-used questionnaire measuring health status (Ware and Sherbourne, 1992). At 5 years (unpublished data) Knutsen et al report continued improvement in the ACI group such that there is no difference between the groups clinically. Nine patients have failed from each group but none of those who had good histology. This indicates that with improvements in cell engineering in the future, results should be better.

A larger randomized trial involving Norwegian and many UK centres is also underway to compare ACI with other treatments. This study is funded by the Medical Research Council and is called ACTIVE (autologous chondrocyte transplantation/implantation versus existing treatments). The ACTIVE trial includes patients with isolated chondral defects on the femoral condyle or trochlea that remain symptomatic following previous treatment.

Discussion

The role of cartilage repair techniques will continue to be debated. Several techniques give reasonable short- and medium-term results but as yet no study has identified a method of cartilage repair that is superior, and further more robust trials are needed to address this question.

Marrow stimulation techniques have the advantage of being easily performed arthroscopically. These techniques may be most suitable for smaller, well-contained lesions. According to Knutsen et al (2004), lesions less than 4 cm^2 are suitable for microfracture treatment. Lesions between 1 and 4 cm^2 may also be suitable for osteochondral autograft transfer. Larger lesions are more amenable to treatment with ACI. The results of randomized trials comparing mosaicplasty with ACI have been variable with one trial in favour of mosaicplasty (Bentley et al, 2003) and one undecided (Smith et al, 2003).

Intense research is underway into second generation tissue-engineering solutions for cartilage repair and regeneration. A number of approaches are being investigated and new techniques will allow arthroscopic implantation of cells, thereby reducing morbidity. Autologous chondrocytes may be delivered on either a matrix or gel. Alternative cell sources such as bone-marrow-derived mesenchymal stem cells are also being investigated and may reduce the possibility of donor-site morbidity. The addition of growth factors or gene vectors into a matrix may stimulate the transformation of the bone marrow cells into chondrocytes.

According to the current National Institute of Health and Clinical Excellence (NICE) guidelines (NICE, 2005), ACI cannot be offered as a primary treatment to any patient in the UK. Appropriate patients need to be enrolled in a properly structured trial to evaluate the effectiveness of this experimental technique in comparison to the other methods. Of the numerous techniques available today, no method has as yet been able to consistently reproduce normal hyaline cartilage, and the best treatment in the long-term is still unknown. The field of cartilage repair will remain controversial for some time to come. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Cartilage defects are difficult to treat.
- Various methods have been advised and tried in the past, but none have proved to be a final solution.
- Autologous chondrocyte implantation has broadened the treatment options for symptomatic chondral defect. But inspite of new advances in the field of tissue engineering, the problem still remains unsolved.