Treatment of articular cartilage defects of the knee

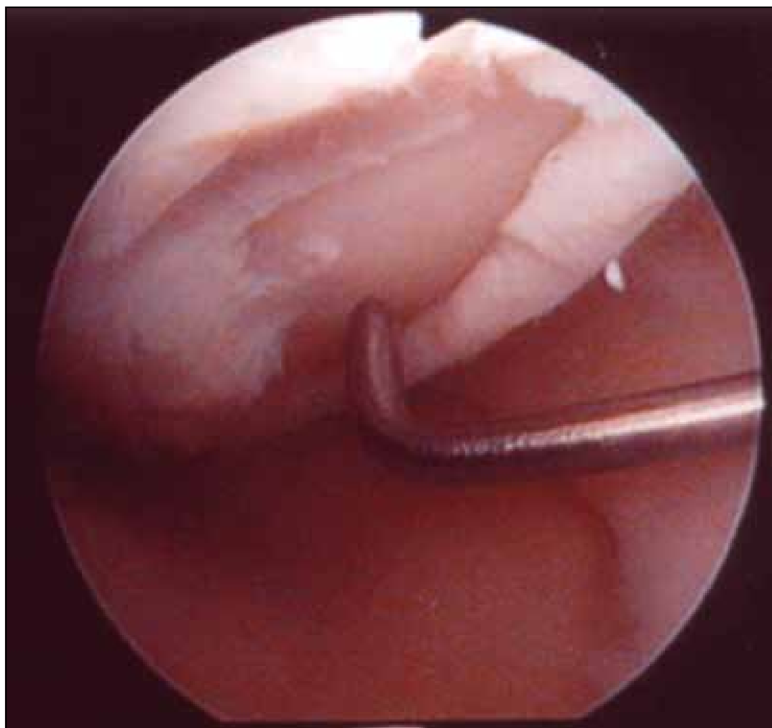
Defects of the articular surface are among the most disabling of all orthopaedic injuries. Many methods of treatment have been used, but these have numerous shortcomings. Consequently, recent research has focused on laboratory-engineered osteochondral tissue.

Cartilage defects are a significant cause of morbidity, occurring in 12% of the population (Basad et al, 2010). Once articular cartilage is injured it has limited capacity for self-repair (*Figure 1*). Surgical techniques fall into three main categories: bone marrow stimulation, substitution techniques and regeneration techniques.

Articular cartilage

Articular cartilage is predominantly composed of extracellular matrix, with only 5% of its volume as cells. Organic material accounts for about 30% of the extracellular matrix, with the remainder being water. Of the organic material 60% is collagen, 25% is hydrophilic proteoglycans, and the remainder is a variety of matrix proteins. Type II collagen makes up 90% of the collagen meshwork. Proteoglycans consist of a central core to which sulphanated glycosaminoglyans (chondroitin sulphate, dermatan sulphate or keratin sulphate) are covalently attached and form a three-dimensional structure. The articular surface provides a smooth surface compatible with frictionless range of motion, and the proteoglycan content resists the compressive forces encountered across the joint under loading.

Figure 1. Osteochondral defects of the knee: arthroscopic view of articular cartilage lesions.



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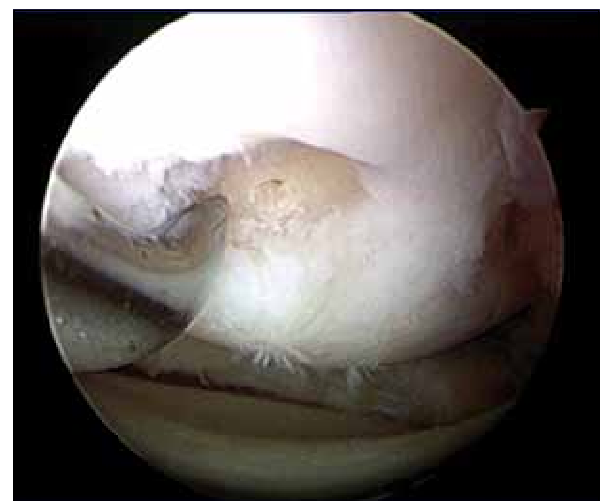
Current treatment options

Bone marrow stimulation: microfracture

Bone marrow stimulation, as its name suggests, is intended to stimulate cell migration and cytokine expression to repair cartilage. Careful use of an 'ice-pick' to open small perforations of the subchondral plate provokes the bone and encourages bleeding. Haematopoietic and mesenchymal stem cells are recruited from bone marrow into the lesion to form new tissue (*Figure 2*).

The new tissue formed is composed of type I, type II, and type III collagen in varying amounts to form fibrocartilage but does not contain sufficient chondrocytes to

Figure 2. Microfracture: arthroscopic view inside the knee joint. Puncture of the subchondral plate allowing bleeding to begin the healing process.



form the hyaline cartilage required to resemble the surrounding tissue. Postoperative rehabilitation and physiotherapy with strict demanding exercise regimens for 6–8 hours daily are initiated immediately and are critically important in the healing process. Despite these limitations it is technically simple, and relatively cheap and quick. It is the technique most widely used by orthopaedic surgeons when repairing small lesions, and also serves as a de facto standard to compare with other modes of treatment.

Between 1986 and 1997, 25 active National Football League players who underwent microfracture surgery for full thickness chondral lesions were followed up for an average of 4.5 years (Steadman et al, 2003). Of these, 19 players (76%) returned to football the season after microfracture. Athletes who returned to football played an average 4.6 seasons (range 1–13 seasons) and 56 games (range 2–183 games) after the procedure.

Similarly, performance outcomes among 24 professional basketball players in the National Basketball Association who underwent microfracture surgery were studied by Cerynik et al (2009). The time required for the players to return to play was 30 weeks (comparable to other studies), but 21% were unable to return to competition. In the first season on return to competition the player's effectiveness and the number of minutes played both dropped and continued to drop year on year.

Gobbi et al (2005) reviewed the results in 53 athletes (26 professional and 27 recreational) with a mean age of 38 years and a mean lesion size of 4 cm^2. At 6 years following microfracture surgery, knee scores measured were normal or nearly normal. The authors found that a greater return to high impact sports was associated with an age of less than 40 years, lesions of less than 2 cm^2, preoperative symptoms of less than 12 months' duration and no prior operative intervention.

Substitution techniques

Autologous osteochondral grafts (mosaicplasty)

This technique was described and developed in Hungary at the beginning of the 1990s and is sometimes referred to as OATS (osteoarticular transfer system). It involves harvesting autologous osteochondral cylinders from less weight-bearing areas of the femoral condyles, transferring them into the defect area and implanting them in a mosaic pattern.

The procedure offers several advantages over other repair techniques, including transplantation of viable hyaline cartilage, a relatively brief rehabilitation period, and the ability to perform the procedure in a single operation. Mosaicplasty seems to be a reliable technique in the short and intermediate term, with better results in young active patients.

Limitations of this technique include limited availability of the graft and possible damage created by harvesting articular cartilage from the healthy area of the joint. Differences in orientation, thickness, graft subsidence and absence of fill with potential dead space between the cylindrical grafts are other limitations of this technique.

Osteochondral allografts

Use of osteochondral allografts avoids the problems associated with grafting in mosaicplasty. This involves transplantation of a cadaveric graft consisting of intact articular cartilage and its underlying subchondral bone into the defect.

Osteochondral allografts can be designed for lesions of any shape or size to achieve precise surface architecture. This eliminates the dead space encountered with mosaicplasty, and can be performed as a single stage procedure with no donor site morbidity.

The allografts must be kept in fresh serum and a reduction in cell viability has been observed when the cultures are kept for more than 72–96 hours, requiring its use within a short period of time (McGoveran et al, 2002). Other limitations include graft availability, high cost, and risk of immune reaction and transmission of disease.

Regeneration techniques

Autologous chondrocyte implantation

Autologous chondrocyte implantation, originally described by Brittberg et al (1994), was an innovative technique in which cartilage defects of the knee were injected with autologous chondrocytes. Initially a biopsy of the affected knee is obtained arthroscopically which is then cultured and expanded to produce chondrocytes of sufficient quantity. In a second operation, the chondrocytes are injected into the defect and covered with a layer of periosteum obtained from the tibia during the same procedure. The periosteal flap is sewn or glued onto the healthy cartilage tissue surrounding the defect (*Figures 3a* and *b*).

In this landmark paper by Brittberg et al (1994) there was a clear link between the formation of hyaline-like cartilage, the quality of the repair tissue and clinical outcome. Autologous chondrocyte implantation has demonstrated good–excellent clinical results in 76–90% of patients (Bentley et al, 2003; Saris et al, 2009; Zaslav et al, 2009) and the results remained stable at 2–10 years follow up (Brittberg, 2008). The advantage of autologous chondrocyte implantation is the demonstration of hyaline cartilage tissue rather than fibrocartilage (offered by microfracture techniques), offering more durable results among athletes and allowing up to 90% of patients to return to sporting activities (Kon et al, 2011).

Autologous chondrocyte implantation requires a two-stage technically demanding procedure, and requires long periods of rehabilitation (9–12 months) to allow the implanted chondrocytes to mature. Risks of complications are low and include morbidity at the periosteal harvest site, graft failure, arthrofibrosis, delamination and tissue hypertrophy, all of which can be substantial and may require further surgical intervention.

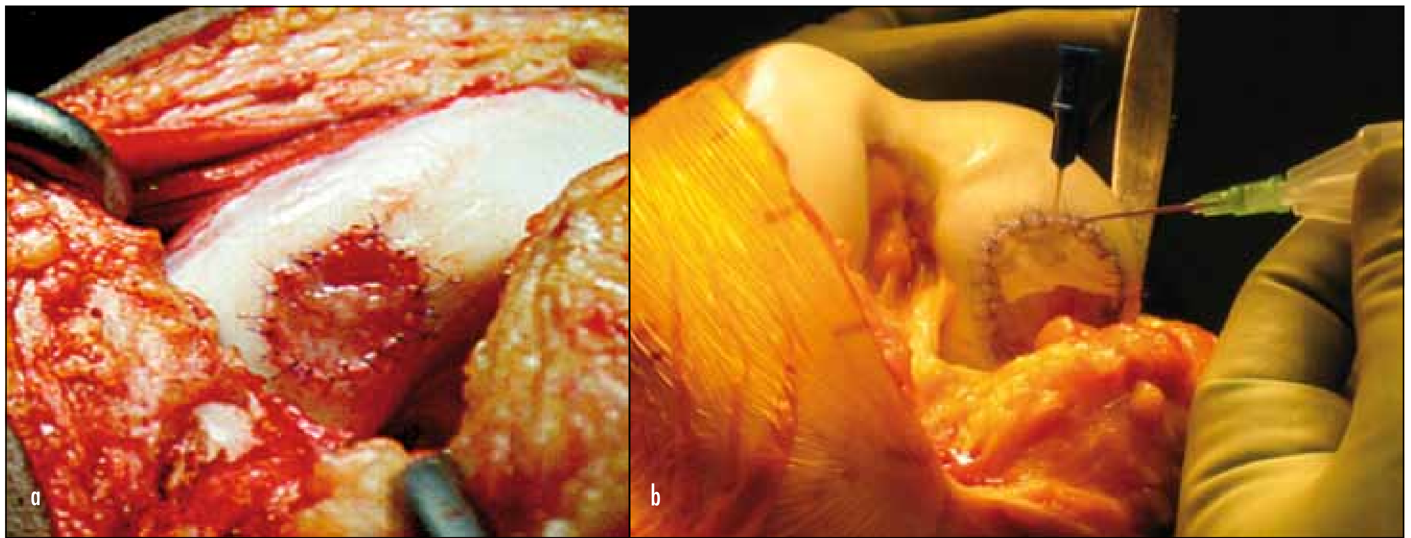


Figure 3. Autologous chondrocyte implantation. a. The periosteal covering is sewn to the surrounding cartilage. b. Chondrocytes are injected into the defect.

Other cell-based and scaffold treatment

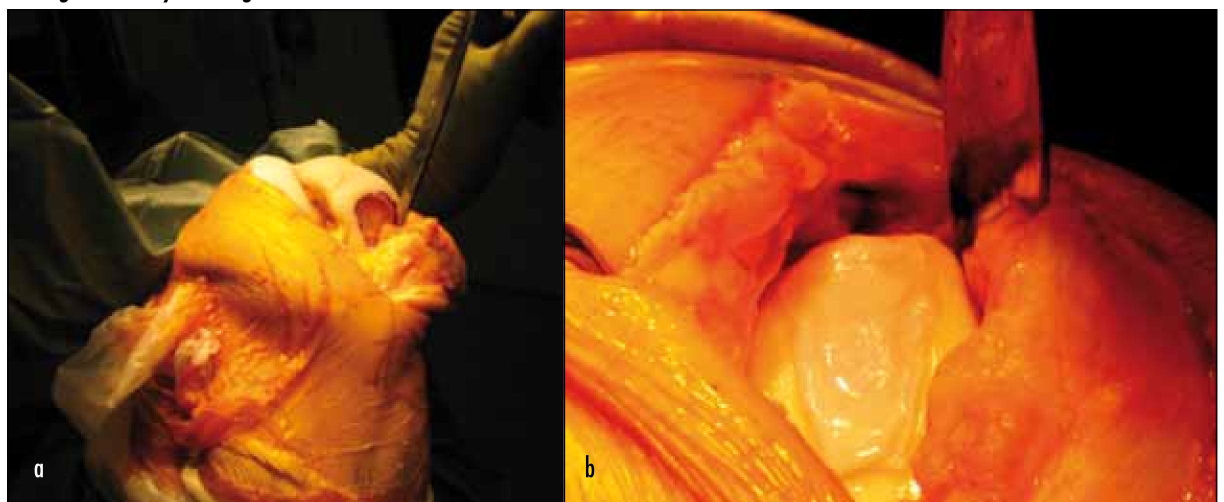
Problems with the first generation autologous chondrocyte implantation techniques have stimulated the development of so-called second-generation techniques known as matrix-associated chondrocyte implantation. Matrix-associated chondrocyte implantation was designed to reduce complications by replacing the periosteal patch with a scaffold matrix seeded with harvested autologous chondrocyte.

These scaffolds were usually composed of either type I collagen, porcine type I/III or hyalouranic acid type matrix. The matrix can be attached to the defect using fibrin glue thereby avoiding micro-suture and disruption of the normal surrounding cartilage (*Figures 4a* and *b*). Hypertrophy rates were reduced to 5% of all cases, and disappeared 3–6 months after the procedure following reabsorption of the membrane (Minas et al, 2010).

Kon et al (2011) compared the clinical outcomes of 41 professional and semi-professional soccer players treated between 2000 and 2006 with a final 7.5-year mean follow up. Twenty-one patients were treated with arthroscopic second-generation autologous chondrocyte implantation and 20 were treated using microfracture. Both treatment methods were successful in 80–86% of patients returning to soccer at a competitive level. Patients treated with microfracture returned to competition 4.5 months earlier than the autologous chondrocyte implantation group, but the results following autologous chondrocyte implantation were more durable whereas the clinical results in the microfracture group deteriorated with time.

In a prospective randomized study by Basad et al (2010) 60 patients who had either matrix-associated chondrocyte implantation or microfracture were followed up for a total of 54 weeks. The outcomes following matrix-associated chondrocyte implantation were significantly superior to microfracture (Lysholm (P=0.005), Tegner (P=0.04), International Cartilage Repair Society

Figure 4. Matrix-associated chondrocyte implantation: (a) before and (b) after attachment. The matrix can be attached to the defect using fibrin glue, thereby avoiding micro-suture.



(ICRS) patient (*P*=0.03) and ICRS surgeon (*P*=0.02) scores) over 24 months. It has been suggested that matrix-associated chondrocyte implantation may prevent chondrocyte de-differentiation during the culturing process, which has been associated with better outcomes.

Two studies comparing first-generation autologous chondrocyte implantation with the second-generation matrix-associated chondrocyte implantation have found no clinical differences between them (Bartlett et al, 2005b; Manfredini et al, 2007). In a randomized study by Bartlett et al (2005a) comparing autologous chondrocyte implantation and matrix-associated chondrocyte implantation, similar functional outcome measures were reported between the two groups. Hyaline-like cartilage or hyaline-like cartilage with fibrocartilage was present in six of the 14 (42.9%) autologous chondrocyte implantation grafts and four of the 11 (36.4%) matrix-associated chondrocyte implantation biopsies; however, the authors did comment on the short follow up of the study. Thus current autologous chondrocyte techniques implant cells with variable chondrogenic potential from a small original cell population and result in inconclusive medium- and long-term results.

When regeneration is effected using first and second-generation techniques, large areas of fibrocartilage tissue are also found, possibly because of their low chondrocyte cellular density and poor proliferative capacity. A promising new approach is the use of tissue engineering applications for the replacement of articular cartilage defects using stem cells in a scaffold and supplemented with growth factors (Hardingham, 2010).

Future direction

Stem cell techniques

Mesenchymal stem cells hold great promise as therapeutic agents in regenerative medicine. The knee microfracture surgery technique popularized by Steadman et al (2003) relies on the release of mesenchymal stem cells for healing and regeneration. These cells are pluripotent cells derived from the mesoderm which reside in multiple human adult tissues including bone marrow, synovial tissue and adipose tissue. Mesenchymal stem cells are capable of differentiating into bone, cartilage, muscle and adipose tissue under appropriate culture conditions (Pittenger et al, 1999). Insulin-like growth factor and transforming growth factor beta-3 (TGF-β3) have been shown to promote chondrocyte differentiation when cultured in a high glucose medium (Yoo et al, 1998).

Mesenchymal stem cells have been isolated from the bone marrow by a small puncture of the iliac crest of patients, but only form 0.001–0.01% of the total nucleated cells in bone marrow aspirates (Phinney and Prockop, 2007). Most research in cartilage regeneration has required the use of culture expansion to get the necessary numbers for clinical application. This method expands cell numbers by 100–10 000 fold over a period of several weeks. The number and lifespan of mesenchymal stem cells within the bone marrow declines with age; similarly, there is a waning differentiation potential with age. Sepsis, wound infection and donor site morbidity are associated complications of this technique.

Extraction of mesenchymal stem cells from knee synovial fat pads has been reported (Dragoo et al, 2003). These cells give a higher yield of adherent colony-forming cells than their bone marrow counterparts. Khan et al (2009) have also shown the differentiation potential of synovial fat mesenchymal stem cells to be maintained in later life.

To date, the use of cultured mesenchymal stem cells to regenerate cartilage has primarily taken place in research with animal models. There have been limited reports of their use in human cartilage repair. One team of researchers published large safety trials into the use of mesenchymal stem cells injected into peripheral joints and intervertebral discs, showing successful regeneration of articular and meniscal cartilage, and with no neoplastic complications (Centeno et al, 2008, 2011).

Scaffolds

There have been a plethora of studies focusing on the use of biomaterial scaffolds, which reconstitute the three-dimensional structural framework of the cartilage matrix and enable the inclusion of expanded cells or growth factors. Scaffolds implanted into the lesion aim to harness and augment the natural host response to injury, provide the volume to fill the cartilage defect and allow cellular proliferation and differentiation, all in an attempt at integration and the provision of more durable repair tissue.

Natural material scaffolds include collagen, fibrin, alginate, agarose, hyaluronan and chitosan. Synthetic material scaffolds include polyactic acid, polyglycolic acid and their derivatives. An important concern is biocompatibility as these materials are broken down by a hydrolytic reaction potentially resulting in inflammation, giant cell reaction and chondrocyte death (Spain et al, 1998).

The Trufit CB osteochondral plug (Smith & Nephew, San Antonio, Texas), made from a polyactic acid and polyglycolic acid derivative and calcium sulphate, has shown good results in clinical trials at 12-month follow up, but longer-term results are awaited (Williams and Gamradt, 2008).

Maioregen is a three-dimensional biomimetic scaffold (MaioRegen, Fin-Ceramica Faenza S.p.A., Italy) (*Figure 5*) obtained by nucleating type I collagen fibrils with hydroxyapatite nanoparticles, in two configurations, bi- and tri-layered, to reproduce chondral and osteochondral anatomy respectively (Kon et al, 2010).

Tissue-engineered collagen matrices seeded with autologous chondrocytes

Third generation techniques, which are very limited at present, propose the mechanical stimulation of the cell-

Figure 5. Maioregen is a three-dimensional biomimetic scaffold (MaioRegen, Fin-Ceramica Faenza S.p.A., Italy) which aims to reproduce chondral and osteochondral anatomy. Mg-Ha = magnesium enriched hydroxyapatite.

scaffold construct with the use of a bioreactor that applies varying hydrostatic pressure to the chondrocytes. NeoCart (Histogenics, Waltham, Massachusetts) is an autologous cartilage tissue-engineered implant that uniquely combines a bovine type-I collagen matrix scaffold with autogenous chondrocytes and bioreactor treatment in a low oxygen tension environment. Early evidence showed improved efficacy over 2 years in a trial comparing the use of NeoCart and microfracture (Crawford et al, 2012).

It is thought that a lack of mechanical stimulation may be the cause of chondrocyte dedifferentiation. The application of a mechanical load stimulates chondrocytes to produce increased amounts of type II collagen, aggrecan, and other critical components of a hyaline extracellular matrix (Tanimoto et al, 2010).

Fourth-generation techniques have also been proposed, which are based on polymers such as elastin, or hydrogels, to obtain a homogeneous three-dimensional distribution of the cells (Kessler et al, 2008). Gene therapy with non-viral genes has also been included, so that the stem cells express the desired growth factors (Vaquero and Forriol, 2012).

KEY POINTS

- Once articular cartilage is injured it has limited capacity for self-repair.
- Treatment aims to restore the normal morphology of the articular surface with the formation of durable hyaline cartilage.
- Surgical techniques fall into three main categories: bone marrow stimulation, substitution techniques and regeneration techniques.
- Microfracture forms new tissue composed of type I, type II and type III collagen in varying amounts to form fibrocartilage but does not contain sufficient quantity of chondrocytes to form hyaline cartilage.
- Microfracture surgery is the most frequently used surgical procedure and is commonly used as a first-line treatment for small cartilage lesions.
- Regenerative techniques such as autologous chondrocyte implantation and matrix-associated chondrocyte implantation have some benefit over microfracture in larger osteochondral lesions but are not without complications.
- New scaffolds and fourth generation regenerative techniques have shown future promise in the treatment of these lesions with good hyaline cartilage formation and durability.

Conclusions

The success of tissue engineering applications can potentially be improved with the addition of adjuncts that increase the proliferation and differentiation of progenitor or stem cells. An alternative cell source that is easy to obtain with a small risk of complications, and has a high cell yield with good proliferation and differentiation potential with no age-related decline, would be ideal to permit optimal cell-based tissue repair therapies in an ageing population. **BJHM**

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Conflict of interest: none.

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