Articular cartilage: structure, injuries and review of management

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Introduction: Chondral and osteochondral injuries are commonly seen in today’s clinical practice. Articular cartilage provides an ultimate low-friction gliding surface, which none of the artificial constructs have been able to replace successfully. Retrospective review of the knee arthroscopies has revealed an underestimated incidence of this complex problem. Cartilage injuries in the knee joint if left untreated lead to pre-mature early arthritis and affect the activities of daily living. Various different treatment methods of cartilage regeneration have shown encouraging results, but unfortunately none has proved to be the ultimate solution.

Sources of data: This article re-visits the intricate structure of articular cartilage and reviews the different methods of regeneration described in the literature, based on evidence-based effectiveness. The methods described by their originators and their results are considered gold standards for those methods, as being the best available evidence.

Areas of agreement: Majority of the authors agree that cartilage injuries are complex and difficult to treat. If untreated, cartilage defects lead to early osteoarthritis. Great debate still persists about the best available treatment for symptomatic chondral or osteochondral defect(s).

Areas of controversy: The controversy about the management outplays its aetiological theories. Several authors have reported good results with different techniques; however none has proved to be the solution for the problem.

Growing points: Up until 1990, marrow stimulation techniques were routine form of management for chondral defects. However, ever since autologous chondrocyte implantation was successfully introduced in humans, it has provided a new dimension for the treatment of chondral defects.

Areas timely for developing research: The success of any treatment lies in its longevity. The new minimally invasive techniques are being invented. However, timely research, on the basis of randomized controlled trial comparing different methods of cartilage reconstruction is necessary for decision-making in today’s evidence-based medical world.
In 1743 William Hunter\textsuperscript{1} stated, ‘an ulcerated cartilage is a troublesome problem and once destroyed, it never repairs’. In spite of new advances in the field of tissue engineering, this statement holds true even three centuries later. Cartilage injuries are common in the knee joint, and if untreated can become symptomatic and progressively lead to premature arthritis. This article revisits articular cartilage anatomy and its injuries and reviews prospective comparative studies between different cartilage reconstruction procedures.

### Anatomy of the cartilage

#### Gross anatomy and types of cartilage

Depending on the composition of the matrix, cartilage in human body is classified into elastic, fibro-cartilage, fibro-elastic and hyaline cartilage. Gliding surfaces of synovial joint are covered with a specialized type of hyaline cartilage, called ‘articular cartilage’. Hyaline cartilage provides a low-friction gliding surface, with increased compressive strength and is known to be wear-resistant under normal circumstances.\textsuperscript{2}

#### Embryology of cartilage

Cartilage arises from mesenchyme. Some mesenchyme cells aggregate to form a blastema, at 5 weeks of gestational age. The cells of blastema begin to secrete cartilage matrix and are then called chondroblasts. With further development, the extracellular matrix that is produced gradually pushes the cells apart. The cells encased in this tough and specialized matrix are called as chondrocytes. The mesenchymal tissue surrounding the blastema gives rise to a membrane called perichondrium.

#### Anatomy of the articular (hyaline) cartilage

Hyaline articular cartilage is aneural, avascular and alymphatic structure.\textsuperscript{2} Chondrocytes form only 1–5\% volume of the articular cartilage. Chondrocytes receive their nutrition by diffusion through the matrix. Matrix pH is 7.4, changes in which can easily disrupt the highly specialized matrix infrastructure. Chondrocytes are very specialized cells responsible for synthesizing and maintaining the matrix infrastructure.\textsuperscript{3}
Composition of articular cartilage

Water: Sixty-five to eighty per cent of wet weight of the cartilage is formed by water, with 80% being in the superficial zone and 65% in the deep zones (Fig. 1A). It allows load-dependent deformation of the cartilage. It provides nutrition and medium for lubrication, creating a low-friction gliding surface. In osteoarthritis, water content becomes more than 90% due to increased permeability and disruption of the matrix. This leads to decreased modulus of elasticity and thus reduction in load bearing capability of the articular cartilage.

Collagen: It forms 10–20% of wet weight of the articular cartilage. Type II collagen forms the principal component (90–95%) of the macrofibrilar framework and provides a tensile strength to the articular cartilage. Table 1 demonstrates all different types of collagens found in articular cartilage and their functions.

Proteoglycans: These protein polysaccharide molecules form 10–20% wet weight and provide a compressive strength to the articular cartilage. There are two major classes of proteoglycans found in articular cartilage, large aggregating proteoglycan monomers or aggrecans and small proteoglycans including decorin, biglycan and fibromodulin. They are produced inside the chondrocytes and secreted in the matrix.

Fig. 1 Ultra-structure of articular cartilage.
The subunits of proteoglycans are called as glycosaminoglycans (GAGs). These are disaccharide molecules, with main two types, chondroitin sulphate and keratin sulphate. GAGs are bound to the protein core by means of sugar bonds, to form aggrecan molecule (Fig. 1B). Link protein stabilizes this chain with a central hyaluronic acid chain to form an intricate structure of the GAG molecule. There are two types (type 4 and type 6) of the chondroitin sulphate. Type 6 remains constant throughout life, whereas type 4 decreases with the age. Aggrecan depletion has been found as an early feature in experimental arthritis.

Proteoglycans maintain the fluid and electrolyte balance in the articular cartilage. These macromolecules have negatively charged sulphate and carboxylate groups, which in turn attract only positively charged molecules and repel the negative molecules. This increases the total concentration of inorganic ions (e.g. sodium) inside the matrix, thereby increasing osmolarity of the articular cartilage, thus creating a Donnan effect.

Chondrocytes (Fig. 1A and C): These highly specialized cells, forming only 1–5% of volume, are sparsely spread within the matrix. Chondrocytes synthesize all the matrix components and regulate matrix metabolism.

Characteristics of chondrocytes are

1. no cell-to-cell contacts, like osteocytes,
2. spheroidal in shape,
3. synthesis of type II collagen and large proteoglycan aggregates and non-collagenous proteins,
4. formation and maintenance of the specialized matrix,
5. high individual metabolic activity, but due to very low overall volume the total activity is low,
6. receives nutrition through double diffusion barrier,
7. cells survive on low oxygen concentration and hence depend on anaerobic metabolism,
8. produce the enzymes responsible for the matrix degradation,
9. mechanical joint loading influences the functions of chondrocytes.

Ultra-structure of articular cartilage

Chondrocytes organize the collagen, proteoglycans and non-collagenous proteins into a unique and highly specialized tissue, suitable for carrying out the functions stated above. The composition, structure and functions of chondrocytes vary depending on the depth from the surface of the cartilage. Morphologically there are four named zones, from top to bottom (Fig. 1D)
1. Superficial zone
2. Transitional zone
3. middle (radial) or deep zone and
4. calcified cartilage zone

Superficial zone

This is the thinnest of all layers, composed of flattened ellipsoid cells. They lie parallel to the joint surface, and are covered by a thin film of synovial fluid, called ‘lamina splendens’² or ‘lubricin’. This protein is responsible for providing an ultimate gliding surface to the articular cartilage. Chondrocytes in this zone synthesize high concentration of collagen and low concentration of proteoglycans, thus making this as the highest water content zone. Parallel arrangement of the fibrils are responsible for providing the greatest tensile and shear strength. Disruption of this zone alters the mechanical properties of the articular cartilage and thus contributes to the development of osteoarthritis. This layer also acts as a filter for the large macromolecules, thereby protecting the cartilage from synovial tissue immune system.

Transitional zone

The cell density in this zone is lower, with predominantly spheroid-shaped cells, embedded in abundant extracellular matrix. The large diameter collagen fibres are randomly arranged in this zone. The proteoglycan aggrecan concentration is higher in this zone.
Middle (radial) zone

Cells are arranged perpendicular to the surface and are spheroidal in shape. This zone contains the largest diameter of collagen fibrils and highest concentration of proteoglycans. However, the cell density is lowest in this zone.

Calcified cartilage zone

This mineralized zone contains small volume of cells embedded in a calcified matrix and thus showing a very low metabolic activity. The chondrocytes in this zone express hypertrophic phenotype. These cells are unique in a way that they synthesize Type X collagen, responsible for providing important structural integrity and provide a shock absorber along with the subchondral bone. The visible border between the third and fourth zones is termed as ‘tidemark’, which has a special affinity for basic dyes, such as toluidine blue. This zone provides an important transition to the less resilient subchondral bone. This zone was considered as an inactive zone, until Hunziker noticed that chondrocytes in this zone were able to incorporate ($^{35}$S) sulphate into pericellular and territorial matrix. Hunziker also speculated that following injury, the metabolic activity in this zone becomes temporarily impaired.

Matrix zones—matrix is organized in three different zones in the cartilage (Fig. 1C)

1. Pericellular
2. Territorial
3. Inter-territorial

Pericellular matrix is a thin rim of matrix-organized issue in close contact with the cell membrane (2-$\mu$m wide). This region is rich in proteoglycans and non-collagenous proteins, like cell membrane-associated molecule anchorin CII, and decorin. It also contains non-fibrillar collagen, made of Type VI collagen.

Territorial matrix surrounds the pericellular region and is present throughout the cartilage. It surrounds individual chondrocytes or a cluster of chondrocytes including their pericellular matrix. In the radial zone, it surrounds each column of chondrocytes. The collagen fibrils in this region are organized in a criss-cross manner thus forming a fibrillar basket surrounding clustered bunch of chondrocytes, protecting them from mechanical impacts.

Inter-territorial matrix forms the most of the volume of all types of matrices, made up of the largest diameter of collagen fibrils. Fibres are oriented differently in different zones, depending on the requirement,
viz. parallel in the superficial zone and perpendicular in the radial zone. This region is distinguishable from others, by formation of aggregates of proteoglycan molecules.

**Functions of hyaline articular cartilage**

Functions of articular cartilage:
1. Provides a low-friction gliding surface.
3. Minimizes peak pressures on the subchondral bone.

Functions of the matrix:\(^2,^7\)
1. Protects the chondrocytes from mechanical loading, thus helping to maintain their phenotype.
2. Storage of some cytokines and growth factors, required for chondrocytes.
3. Determines the type, concentration and rate of diffusion of the nutrients to chondrocytes.
4. Acts as a signal transducer for the cells.

Matrix deformation produces mechanical, electrical and chemical signals, affecting the functions of chondrocytes. Thus, matrix also plays a role in recording a loading history of the articular cartilage.

**Natural history of chondral injuries**

*Epidemiology of cartilage injuries*

A recent review of 993 arthroscopies, using International Cartilage Repair Society (ICRS) scoring system,\(^8\) reported 66% articular cartilage pathologies, with 11% full thickness chondral lesions being suitable for the cartilage regeneration techniques. Another retrospective study of 31 000 arthroscopic procedures revealed\(^9\) 63% incidence of cartilage defects. Both these large-scale studies highlighted an underestimated incidence of such a complex problem. However, there is still a great debate about an optimum treatment of symptomatic chondral defects in the knee joint.

In Johnson-Nurse and Dandy’s series (Cambridge)\(^10\) of 72 knee injury patients, 95% presented with pain, 76% with swelling and 18% with locking, with history of trauma in 68% of patients. The authors concluded that articular cartilage lesions were most commonly seen during the fourth decade of life, with full thickness lesions common in young adults in their third decades, following acute traumatic injuries. Repetitive minor trauma and major overt injuries can lead to osteoarthritis.\(^4,^11\)
Typical symptoms of chondral injury are similar to meniscus tear, like swelling, local pain, locking, pseudo-locking and catching. Outerbridge has classified these focal chondral defects into different stages, based on the severity of the defect. However, such large focal defects, if left untreated, ultimately lead to premature end-stage arthritis. The most commonly available treatment for end-stage knee osteoarthritis is prosthetic replacement of the articular surface, termed as total knee arthroplasty. However, this treatment is suitable for the elderly people more than 60 years of age, with a sedentary life style. Thus, patients younger than 45 years of age are not ideal candidates for the total knee replacement.

Repair and regeneration of chondral injuries

For the past three centuries, physicians and scientists have sought several different ways to repair or regenerate articular surface of synovial joint following traumatic damage or degeneration of the cartilage. Repair refers to the restoration of a damaged articular surface with a neo-cartilage tissue, which resembles to the native cartilage, but does not necessarily duplicate its structure, composition and function. Regeneration refers to the formation of tissue, indistinguishable from the native articular cartilage.

A typical tissue response to injury follows a cascade of necrosis, inflammation, repair and scar remodelling. Vascular phase of this cascade is the most important determinant of healing. Hyaline cartilage, being avascular structure, lacks an ability to generate this vital response. Thus, after any mechanical insult or damage, the intrinsic reparative ability of cartilage is very low. Healing of the cartilage defect means restoring structural integrity and function of the damaged tissue.

Natural history of cartilage injuries is not well understood, but what we do know may help us to identify which patients to treat. While isolated cartilage defects in the knee were found in 4% diagnostic arthroscopies, a considerable higher percentage (40–70%) has been described in knees with meniscus and/or ligamentous injuries. Cartilage injuries can be divided in two broad categories.

1. Direct mechanical trauma to the matrix, without damaging the cells: In this situation, if the loss of matrix components does not exceed the ability of chondrocytes to synthesize new proteoglycan molecules, cartilage will be restored.

2. Mechanical destruction of the cells and matrix, due to blunt or penetrating trauma: This is the most commonly seen situation in clinical practice. Results of the repair depend on several different factors.
Factors associated with repair response

Depth of the defect
Depending on the depth, articular cartilage defect is classified as chondral or osteochondral. The pure chondral defect is further divided into a full thickness, i.e. down to subchondral bone or a partial thickness or a flap of cartilage\(^5\) (Fig. 2E). These defects increase in size and depth and do not repair on their own.\(^5,11,18\) Result of repair depends on whether the injury extends down to the subchondral vascular bone marrow. Osteochondral defect consists of a full thickness cartilage defect extending into the underlying subchondral bone (Fig. 2F). Thus, osteochondral defect crosses the tidemark, making way for the bone marrow mesenchymal progenitor cells into the defect. This leads to the formation of a fibrocartilage type of repair. Hence, depth of the defect is crucial for stimulating a repair response.

However, several studies\(^5,19,20\) have shown that this repair tissue is biomechanically and structurally inferior to the hyaline cartilage, and thus may not be suitable for a load-bearing function.

Size of the defect
Size of the defect is an important factor in the repair response. Study in horses\(^21\) has revealed that defects <3 mm in diameter may lead to complete repair after 9 months, whereas larger defects do not repair completely. Repair response of articular cartilage depends on the extent of injury, measured by volume and surface area of the defect. The defects <1 cm\(^2\) in diameter are less likely to affect stress distribution on the subchondral bone, and probably will not progress.

Age
Age is a stronger risk factor for development of osteoarthritis. Aging reduces the cartilage hydration and population of chondrocytes in the cartilage. Mitotic and synthetic activities of chondrocytes decline with age.\(^5,18\) Animal studies in rabbits have demonstrated a better reparative

![Fig. 2 Classification of cartilage defects.](image-url)
response for 2 mm chondral defects in younger animals (5 weeks) than the older ones (4 months).19

Depth of injury is found to be age-related. Children and adolescents develop osteochondral lesions, whereas adults get pure chondral lesions, possibly because of the well-developed and matured calcified zone.10 Though osteochondral lesions (osteochondritis dissecans—OCD) in the children with growing bones (open physis) usually heal without any problem; adult form of OCD rarely heals.21

**Trauma**
Sudden heavy impact to the joint surface or repetitive loading of the articular cartilage can cause microdamage to the chondrocytes, leading to cellular degeneration and cell death. This also causes disruption of the collagen matrix leading to increased hydration, fissuring in the cartilage and thickening of the subchondral bone.22 Trauma also leads to decreased production of proteoglycans by the chondrocytes. And even though an outer surface of cartilage appears to be intact, the actual cartilage tends to be softer and fimbrillated on indentation.

**Mechanical malalignment of the joint**
Abnormal loading of the joint in turn leads to excessive focal stresses on the cartilage leading to early degeneration.5,18,22 The location of defect (whether loaded or unloaded) does influence repair response of the cartilage. This forms the basis for corrective osteotomy around the knee joint. Cartilage behaves differently in loading response. Immobilization or reduced loading leads to decrease in aggregation and synthesis of GAGs, which can be reversible up to a certain limit. Immobilization also leads to a reduction of smaller proteoglycan molecules and irreversible disruption of collagen fibres.

Though the evidence in available literature varies between the patient groups, it is very much clear that the regenerated tissue does not duplicate exact composition, structure and mechanical properties of this highly specialized bearing surface. However, it seems that regeneration of entirely normal cartilage may not be the prerequisite, as majority of techniques have shown significant improvement in the patient symptoms and joint movements (usually more than 75%), in spite of neo-cartilage not being the exact replacement for the native articular cartilage.5,11

**Surgical treatment of the cartilage defects**

**Bone marrow stimulation**
Penetration of subchondral bone is among the oldest and still the most commonly used method to stimulate regeneration of neo-cartilage. As
the name suggests, this method is suited for a full thickness chondral defect with an exposed subchondral bone. Penetration of subchondral bone plate disrupts the subchondral blood vessels. This leads to the formation of a ‘super clot’ or fibrin clot on the surface of a chondral defect. If the defect is protected from loading at this stage, then the primitive bone marrow mesenchymal stem cells migrate into the super clot, to proliferate and differentiate into the cells, resembling morphologically with the chondrocytes.

**Joint debridement and drilling**

Joint debridement was originally described by Magnuson (Fig. 3B).\(^{23}\) It was a broad term, which included articular trimming, meniscectomy, removal of osteophytes and loose bodies, articular abrasions and even synovectomy.\(^{24}\) The combined effect of all these procedures together on the outcome of chondral defect was difficult to quantify. Secondly, the results of such treatments were influenced by the size, number and degeneration of chondral defects presented. Pridie\(^{25}\) described a drilling of the subchondral bone, preceded by careful removal of all the loose pieces of cartilage. In clinical practice, joint debridement is usually combined with other marrow stimulation techniques, such as drilling or microfracture. Thus, debridement should be considered as a Part I of any marrow stimulation techniques.

In a randomized, controlled trial described by Hubbard, a simple excision of loose fragments versus simple washout, revealed a significant improved functional results for up to 5 years, with 65% patients pain-free.\(^ {24}\) This study included isolated focal chondral defects on medial femoral condyle, treated with removal of all the surrounding unstable cartilage, followed by the abrasion of the exposed calcified cartilage layer. The debridement group had significant improvement over lavage as measured by Lysholm score.\(^ {26}\) Results gradually deteriorated over the 5-year period. Studies of debridement in osteoarthritis have conflicting conclusions.\(^ {27,28}\) Opinions are divided as to whether arthroscopic debridement has any place in the treatment of established osteoarthritis, but this debate is not relevant to the treatment of localized symptomatic chondral defects.

**Fig. 3** Methods of cartilage regeneration.
**Spongialization**

This method is a modification of debridement and drilling, being more radical one. Ficat described this term, which involved excision of damaged cartilage along with the involved subchondral bone. He reported 79% good-to-excellent results in a series of 85 patients, with degenerative defects in patella.\(^{29}\)

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**Microfracture**

Microfracture, a modification of Pridie’s drilling method, is a simple arthroscopic and by far the commonest method used as a first-line treatment for symptomatic chondral defect(s) (Fig. 3C). Rodrigo et al. reported good improvement in functional outcomes of patients with chondral defect, treated with a combination of debridement and microfracture.\(^{30}\) However, the credit of describing microfracture as an isolated treatment for symptomatic chondral defect goes to Steadman et al.\(^{31}\) In this procedure, all the unstable cartilage is removed to create a stable well-contained defect surrounded by normal cartilage, with a complete exposure of the subchondral plate. The success of this procedure lies in creating stable perpendicular edges of healthy cartilage around the defect. An arthroscopic awl is then used to create iatrogenic but controlled multiple fracture holes penetrating the subchondral plate of bone, 3–4 mm apart. Importantly, the integrity of the subchondral bone plate has to be maintained. The defect gets filled in with a so-called ‘super clot’, an optimal environment for pluripotent marrow cells to differentiate into a stable repair tissue. Early mobilization with continuous passive motion, followed by strictly protected weight-bearing programme, is mainstay in the success of the outcome following microfracture therapy.

Advantages of microfracture over drilling might be that there is no over-heating or burning of subchondral bone and that a rougher surface is produced, making it easier for repair tissue to adhere. In addition, it is easier to penetrate the defect perpendicular to the surface.

Though Hunziker reported longevity of this method for up to 5 years,\(^{32}\) study by Steadman et al. suggests favourable outcome of up to 7 years. Second, this study also revealed better results in patients <35 years than between 35 and 45 years of age.\(^{33}\) Knutsen et al.\(^{34}\) compared the results of microfracture with ACI in a randomized controlled trial, with 11.4% (out of 20) biopsies being predominantly of hyaline and 17.1% being fibro-hyaline in nature.

Microfracture, being an arthroscopic day-case procedure, is the most popular treatment among the sportsmen, as revealed by one study in national football league players, with 76% players who are able to get back to the game next season.\(^{35}\) Though this method is technically easier and less invasive, the neo-cartilage surface formed has been found to be
biomechanically inferior and less durable as compared with the hyaline cartilage.22

**Mosaicplasty**

Mosaicplasty was first described in 199336 and since then widely used for treating chondral and osteochondral defects (Fig. 3A). In this technique, cylindrical osteochondral plugs are harvested from a low-weight-bearing areas within the knee joint. The chondral defect is prepared, with perpendicular vertical edges of normal cartilage around. The osteochondral plugs are used to fill the chondral defect to create a ‘mosaic’ pattern hence called as mosaicplasty. Various sizes of the plugs are used to get maximum fill of the defect. The gaps between the plugs get filled in by fibrocartilage. The original technique was an open procedure. Hangody37 described a mini open approach for the mosaicplasty, especially for the larger defects, patellar defects and defects on femoral condyle not easily accessible through arthroscopy. However, recent developments in instrumentation and surgical techniques have made it possible for this procedure to be done as an arthroscopic day case procedure.

The proponents of this technique boast an advantage of this technique in providing a stable, firm weight-bearing surface. The gaps between the plugs are usually filled in by fibrocartilage derived from the debrided base of the chondral defect, providing secondary stability to the plugs.38,39 However, many authors have described these spaces as ‘dead spaces’, providing lower stability to the plugs.38,39

There is always an issue about the donor site morbidity, but Hangody39 recommends avoiding the donor site morbidity by limiting the defect treated area to be 1–4 cm². Disadvantages of this procedure are technical difficulty, special equipment, inability to restore congruous surfaces, differences in cartilage heights of the defect and surrounding native cartilage.

The main reason for disrepute of this procedure was lack of lateral integration of the mosaic plugs with that of a native cartilage, as the synovial fluid leak leads to the cyst formations at the bottom, making healing unlikely. Secondly, it is technically difficult to use this procedure for the tibial chondral defects. Bentley *et al.* raised the concern about the use of this technique in patellar defects, with fair or poorer results in their series.41

The largest published series of mosaicplasty by Hangody *et al.*37 consisted of 597 defects on femoral condyles, 118 patellofemoral joints and 76 tibial condyles and the follow-up dated back up to 10 years. In this series, good-to-excellent results are reported in 92, 87 and 79% of patients undergoing mosaicplasty of the femoral condyle, tibial plateau and patello-femoral joints, respectively. However, the mean time to
follow-up period had not been revealed in this paper and thus had not reflected on the survival of osteochondral plugs in those patients with the longest follow-up.

**Carbon fibre implants**

Carbon fibre rods and pads had been used to treat chondral and osteochondral defects, mainly acting as scaffolds to direct regeneration of the neocartilage on to the joint surface. Bentley et al. commonly used the carbon fibre implants to treat patellar defects but reported the success rate of only 41%, with poor quality fibrous tissue covering the implant surface. However, no histological analysis was reported. Introduction of a non-absorbable material just deep to the subchondral bone had been a debatable issue for its disrepute.

Brittberg et al. used carbon fibre implants for treating early osteoarthritis, with 83% success rate in 37 treated patients. The end-stage or advanced osteoarthritis might be the only indication these days, with knee replacement being the next option.

**Perichondrial grafts**

Homminga et al. used autologous strips of perichondrium to treat the chondral defect, with fibrin glue acting as an adhesive. Long-term results of 88 patients with a mean follow-up 52 months demonstrated good results in only 38% of patients (Hospital for Special Surgery Score). Histological analysis of 22 biopsies revealed satisfactory results in only 6 (27%) biopsies, showing hyaline-like morphology.

**Periosteal grafts**

Periosteum has a potential for both chondrogenesis and osteogenesis, making it an ideal biological membrane for repair of the chondral defects. Alfredson highlighted importance of continuous passive motion (CPM) in 57 patients treated for patellar defects. Of the 38 patients who used CPM postoperatively, excellent or good results were seen in 76% patients at a mean follow-up of 51 months. Of the 19 patients who did not use CPM in the immediate post-operative period, 53% were graded as excellent or good at a mean follow-up of 21 months. Calcification of the grafts had been mentioned as a problem in the long term.

**Osteotomy**

Osteotomy is usually reserved for early uni-compartmental osteoarthritis. Osteotomy redistributes the joint load and thus avoids contact
pressure loads on the cartilage surface, thereby decreasing the rate of cartilage degeneration. In a prospective series of 95 medial compartmental osteoarthritis patients, Schultz and Gobel\textsuperscript{47} compared the effect of isolated osteotomy against the debridement or drilling of associated chondral defect in the degenerate compartment. Follow-up arthroscopy and biopsy revealed better coverage of degenerate cartilage by forming a thicker repair tissue when osteotomy was combined with drilling or debridement. Patients in this series reported improvement in walking distance and knee extension. Another study by Kanamiya \textit{et al.}\textsuperscript{48} revealed a good correlation between the amount of correction achieved and visible improvement in the articular surface, with almost 60\% femorotibial joint surface being covered with new fibrocartilage repair tissue. One such study involving 146 knees in 115 patients treated with high tibial osteotomy revealed formation of hyaline-like or good quality cartilage in 32\% knees, with 59\% showing partial repair response. Surprisingly, the study also revealed a higher chance for a good quality repair response in cases treated with over correction, possibly leading to increased off loading of the affected compartment.\textsuperscript{49}

**Autologous chondrocyte implantation (Fig. 4)**

The technique of autologous chondrocyte implantation (ACI) was first described by Peterson \textit{et al.}\textsuperscript{50} from Gothenburg during 1984–1987, and this was the first ever application of ‘tissue engineering’ in orthopaedic surgery. In this approach, a small cartilage piece is harvested from a low-weight-bearing area of the knee joint. The chondrocytes are enzymatically isolated under all aspetic technique in a specialized tissue culture laboratory. The cells are then grown \textit{in vitro} under the most optimal conditions, to create millions of active chondrocytes. After 2–3 weeks, the joint is opened and the chondral defect is covered with a periosteal patch from the upper tibial surface. After achieving a water-tight seal, the cell suspension is injected underneath this patch (Fig. 4). The initial experimental studies were undertaken in rabbits, with successful reduplication of the results in humans. This original technique described by Brittberg and colleagues is considered as a cell-based therapy. The subsequent generations of ACI involving scaffolds and growth factors are considered as tissue-engineering techniques.

Brittberg \textit{et al.}\textsuperscript{51} presented the results of first 23 patients, with mean follow-up of 39 months. In this series, good or excellent clinical results were reported in 70\% of cases (88\% of femoral condylar defects). Of the biopsies from treated femoral condyle lesions, 11/15 had a ‘hyaline-like’ appearance. More recent publication from this group have shown durable results up to 11 years and good results following treatment of
osteochondral lesions. Gothenberg group has reported good-to-excellent results of up to 89% in focal well-contained chondral defect. One other study also has demonstrated good results comparable with the original studies.

The histological studies following ACI surgery had revealed that the repair tissue response was ‘hyaline-like’, or ‘predominantly hyaline’ in some specimens. However, the best repair tissue produced in these series was not morphologically or histo-chemically identical to normal hyaline cartilage, and fibrocartilage was often found in a proportion of samples. This however was labelled as a good-quality fibrocartilage.

In a randomized controlled trial comparing ACI against microfracture group Knutsen reported no correlation between the histology and the clinical outcome in either of the two groups at 2 years following the surgery. The recent five-year follow-up study of these patients revealed that none of the patients with the best-quality cartilage (predominantly hyaline) at the 2-year mark had a later failure. Both ACI and microfractures were found to be comparable at a 5-year mark, with 77% success rate. However, long-term follow-up is required to assess the progression of osteoarthritis and confirm which of the two methods is better than the other one.

In a recent randomized controlled trial, comparing ACI versus microfracture Saris et al. reported better results in chondral defects treated with characterized autologous chondrocytes than microfracture group, revealed by better structural repair assessed by histomorphometry and overall histological evaluation. Though the clinical scores were comparable in both groups, tissue regeneration was superior in ACI group.
Long-term follow-up is again required to ascertain the survival of the ACI graft.

As a variation of the ACI technique, Wakitani et al.\textsuperscript{57} used culture-expanded bone marrow mesenchymal stem cells instead of the chondrocytes to regenerate the repair tissue. This technique could be combined with a high tibial osteotomy. The main advantage of this technique was preservation of normal surrounding cartilage.

In spite of so many different treatment methods described, none of the above method has been able to regenerate a neo-cartilage similar in structure and functions to that of a native articular cartilage. A recent focus on the autologous chondrocytes implantation revealed a long-term durability of up to 11 years, highlighting a potential of this cell-based therapy in finding an ultimate solution for this complex problem. Various different modifications of autologous chondrocytes implantation are currently being tried out, focussing especially on the minimally invasive surgery, and combination of ACI with threedimensional scaffolds and growth factors.

References


