

# Regeneration of Articular Cartilage of the Knee: Basic Concepts

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E. Carlos Rodríguez-Merchán  
and Hortensia De la Corte-García

## 1.1 Introduction

Cartilage injury of the knee is common and its aetiology is multifactorial (Table 1.1) (Fig. 1.1). One study of knee arthroscopy found 63 % of patients had chondral injury [1]. Cartilage injuries of the knee affect approximately 900,000 Americans annually, resulting in more than 200,000 surgical procedures [2].

The Outerbridge classification of articular cartilage lesions is most commonly used (Table 1.2) [3]. For the patient with symptomatic chondral injury of the knee, numerous techniques are available to the orthopaedic surgeon to relieve pain and improve function (Tables 1.3, 1.4 and 1.5). Although nonsurgical management of articular cartilage injury has remained largely the same over many decades, surgical treatment of chondral injuries continues to evolve. Although

bone marrow stimulation techniques continue to play a large role in the treatment of specific chondral injuries, newer techniques including autologous chondrocyte implantation (ACI), osteochondral allografts, and osteochondral autografts have been developed. Treatment decision-making must take into consideration patient goals, physical demands, expectations, and perceptions, as well as defect size, depth, location, chronicity, previous treatments and response, and concomitant pathology [4].

Cartilage therapy for focal articular lesions of the knee is becoming increasingly available [5, 6]. Cellular and molecular studies using new technologies such as cell tracking, gene arrays and proteomics have provided more insight in the cell biology and mechanisms of joint surface regeneration. Besides articular cartilage, cartilage of other anatomical locations as well as progenitor cells are now considered as alternative cell sources. Growth factor research has revealed some information on optimal conditions to support cartilage repair. Thus, there is hope for improvement [7].

The aging human population is experiencing increasing numbers of symptoms related to its degenerative articular cartilage, which has stimulated the investigation of methods to regenerate or repair articular cartilage. However, the seemingly inherent limited capacity for articular cartilage to regenerate continues to confound the various repair treatment strategies studied [8].

PubMed articles related to articular cartilage regeneration of the knee in clinical studies were searched from 1 January 2005 to 31 December

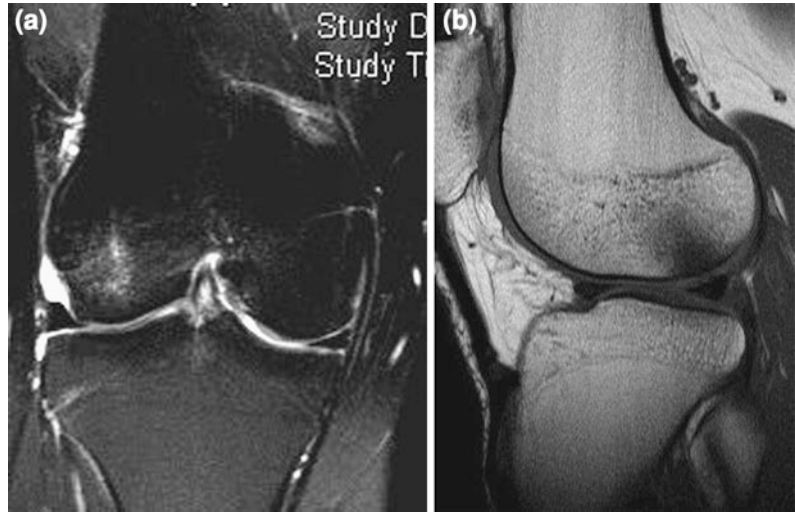
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E. C. Rodríguez-Merchán (✉)  
Department of Orthopaedic Surgery,  
“La Paz” University Hospital-IdiPaz,  
Paseo de la Castellana 261, 28046  
Madrid, Spain  
e-mail: ecrmerchan@gmx.es

E. C. Rodríguez-Merchán  
School of Medicine, “Autónoma” University,  
Madrid, Spain

H. De la Corte-García  
Department of Physical Medicine and  
Rehabilitation, “12 de Octubre”  
University Hospital, Avenida de Córdoba s/n  
28041 Madrid, Spain  
e-mail: hortensia.corte@yahoo.es

**Fig. 1.1** MRI of a cartilage injury of the knee.  
a AP view. b Lateral view



**Table 1.1** Aetiology of articular cartilage lesions of the knee

|                                                                                |
|--------------------------------------------------------------------------------|
| Trauma (blunt impacts, traumatic patellar dislocation, polytraumatic injuries) |
| Axial malalignment of the knee                                                 |
| Partial or total meniscectomy                                                  |
| Instability (ACL, PCL, etc.)                                                   |
| Osteochondritis dissecans                                                      |
| Osteoarthritis                                                                 |
| Rheumatoid arthritis                                                           |
| Genetic factors                                                                |
| Obesity                                                                        |
| Cartilage tumours                                                              |
| Microtrauma                                                                    |

**Table 1.2** Grade 0–4 cartilage defects, according to the Outerbridge scale

|         |                                                                |
|---------|----------------------------------------------------------------|
| Grade 0 | Intact articular cartilage                                     |
| Grade 1 | Cartilage softening, intact joint surface, focal colour change |
| Grade 2 | Superficial fissuring                                          |
| Grade 3 | Fissures and fragmentation extending into the matrix           |
| Grade 4 | Erosion reaching the subchondral bone plate. Eburnated bone    |

**Table 1.3** Conservative treatment of articular cartilage defects of the knee

|                                                                                                 |
|-------------------------------------------------------------------------------------------------|
| <i>Drug treatment</i>                                                                           |
| NSAIDs per os                                                                                   |
| Neuroceticals (glucosamines per os, intra-articular cortisone, intra-articular hyaluronic acid) |
| <i>Physical therapy</i>                                                                         |

**Table 1.4** Operative interventions capable of covering a knee cartilage defect completely

|                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Refixation of detached cartilage fragments</i>                                                                                         |
| With reabsorbable pins                                                                                                                    |
| With screws                                                                                                                               |
| With fibrin glue                                                                                                                          |
| With osteochondral plugs                                                                                                                  |
| <i>Cartilage reparative strategies</i>                                                                                                    |
| Aggressive debridement (spongialisation): removal of the subchondral plate to expose cancellous bone                                      |
| Bone marrow stimulation techniques: drilling, microfractures, abrasion arthroplasty (gentle superficial burring of the subchondral plate) |
| <i>Cartilage restorative techniques</i>                                                                                                   |
| Transplantation of fresh osteochondral allografts                                                                                         |
| Transplantation of osteochondral autografts (plugs—mosaicplasty)                                                                          |
| Autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI)                                   |

**Table 1.5** Indications for the different knee cartilage repair/restorative techniques

| Technique                                                                                               | Indications                                                                                       |
|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Bone marrow stimulation                                                                                 | Lesion size < 4 cm <sup>2</sup> ; age < 40 years; focal contained lesions in the femoral condyles |
| Transplantation of fresh osteochondral allograft                                                        | Large uncontained lesions and lesions with bone and cartilage loss                                |
| Transplantation of osteochondral autograft (plugs—mosaicplasty)                                         | Femoral lesions < 2.5 cm <sup>2</sup>                                                             |
| Autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI) | Chondral lesions > 2 cm <sup>2</sup>                                                              |

2011, using the following key words: articular cartilage, regeneration, clinical studies and knee. A total of 53 reports were found. They showed the following possibilities for the treatment of focal lesions of the articular cartilage of the knee: cartilage regeneration and repair including cartilage reparation with gene-activated matrices (GAM), autologous chondrocyte implantation (ACI) and matrix-induced ACI (MACI), biological approaches (scaffolds, mesenchymal stem cells-MSCs, platelet-rich plasma-PRP, growing factors-GF, bone morphogenetic proteins-BMPs, magnetically labelled synovium-derived cells-M-SDCs, elastic-like polypeptide gels), osteotomies, stem cells coated titanium implants and chondroprotection with pulsed electromagnetic fields (PEMFs). Meniscal repair still is in an experimental phase. There is also new information on topics like the specific healing response of cartilage lesions, cartilage healing in patellar fractures, the importance of surgical preparation, the prognostic factors involved in cartilage regeneration and the assessment of results.

The purpose of this chapter is to summarise the existing knowledge on regeneration of articular cartilage of the knee based on the clinical studies published since January 2006–31 December 2011. In this chapter the author will review what is the current treatment of focal cartilage lesions of the knee joint, and what is known on meniscal

repair and other related topics such as the specific healing response of cartilage lesions, cartilage healing in patellar fractures, the importance of surgical preparation, the prognostic factors involved and the assessment of results.

## 1.2 Treatment of Focal Cartilage Lesions

There are a number of possibilities for the treatment of focal lesions of the articular cartilage of the knee: (1) cartilage reparative strategies such as aggressive debridement and bone marrow stimulation (drilling, microfractures); (2) cartilage restorative techniques such as fresh osteochondral allograft transplantation, osteochondral autograft transplantation (mosaicplasty); (3) autologous chondrocyte implantation (ACI) or matrix-induced ACI (MACI); (4) Some biological methods such as cartilage reparation with gene-activated matrices (GAMs), scaffolds, mesenchymal stem cell (MSCs), platelet-rich plasma-PRP, growing factors (GFs), magnetically labelled synovium-derived cells (M-SDCs), bone morphogenetic proteins (BMPs) and elastic-like polypeptide gels; and (5) other techniques, such as osteotomies, stem cells coated titanium implants in osteochondral defects and chondroprotection with pulsed electromagnetic fields (PEMFs).

Simon and Aberman reported animal models and described two untreated lesion models useful for testing articular cartilage repair strategies [8]. The created lesion models, one deep (6 mm and through the subchondral plate) the other shallow (to the level of the subchondral bone plate) were placed in the middle one-third of the medial femoral condyle of the knee joints of goats. At 1-year neither the deep nor the shallow full-thickness chondral defects generated a repair that duplicated natural articular cartilage. Moreover, progressive deleterious changes occurred in the articular cartilage surrounding the defects.

### 1.2.1 Cartilage Reparative Strategies

Shim et al. reported that microfracture therapy is a widely used technique for the repair of

articular cartilage defects because it can be readily performed arthroscopically [9]. However, the regenerated cartilage after microfracture surgery clearly differs from normal articular cartilage. This suggested that the clinical outcome of patients undergoing microfracture therapy could be improved. Dehydroepiandrosterone sulphate (DHEA-S) is known to protect against articular cartilage loss. Therefore, in an effort to achieve cartilage regeneration of high efficacy, they manufactured a DHEA-S-releasing rod-type implant for implantation into the holes produced by microfracture surgery. The polymeric rod-type implant was made of biodegradable poly (D, L-lactide-co-glycolide) (PLGA) and beta-tricalcium phosphate to enable controlled release of DHEA-S. The implant was dip-coated with a dilute PLGA solution to prevent the burst release of DHEA-S. This polymeric rod-type implant did not only provide an improvement in microfracture surgery, but also had great potential as a new formulation for drug delivery.

Bae et al. evaluated the clinical and radiologic results, second-look arthroscopic findings, histologic evaluation, and results of immunohistochemical staining and the Western blotting test for type II collagen after microfracture for full-thickness chondral defects in patients with osteoarthritic knee [10]. They concluded that patients with full-thickness chondral defects in the osteoarthritic knee can have improved function and see an increase in joint space after microfracture. They also showed that cartilaginous tissue containing type II collagen is formed after the microfracture procedure in the osteoarthritic knee.

### 1.2.2 Cartilage Restorative Strategies

Fresh osteochondral allograft transplantation has been an effective treatment option with promising long-term clinical outcomes for focal posttraumatic defects in the knee for young, active individuals. Gross et al. examined histologic features of 35 fresh osteochondral allograft specimens retrieved at the time of subsequent graft revision, osteotomy, or TKA [11]. Graft survival time ranged from 1 to 25 years based on their time to

reoperation. Histologic features of early graft failures were lack of chondrocyte viability and loss of matrix cationic staining. Histologic features of late graft failures were fracture through the graft, active and incomplete remodelling of the graft bone by the host bone, and resorption of the graft tissue by synovial inflammatory activity at graft edges. Histologic features associated with long-term allograft survival included viable chondrocytes, functional preservation of matrix, and complete replacement of the graft bone with the host bone. Given chondrocyte viability, long-term allograft survival depends on graft stability by rigid fixation of host bone to graft bone. With the stable osseous graft base, the hyaline cartilage portion of the allograft can survive and function for 25 years or more.

Ollat et al. evaluated the results and prognostic factors cartilage defects of the knee treated by autologous osteochondral mosaicplasty after more than five years of follow-up [12]. Autologous osteochondral mosaicplasty seemed to be a reliable technique in the short and intermediate term. It has the advantage of being less expensive than reconstructive techniques, is a one-step surgical procedure and results in immediate restoration of cartilage surface. Nevertheless, this is a difficult technique, which may result in complications and requires articular harvesting. This technique is limited by the size of the defect to be treated. The primary indication is deep, small defects on the medial femoral condyle.

### 1.2.3 Autologous Chondrocyte Implantation (ACI) and Matrix-Induced Chondrocyte Implantation (MACI)

Gigante et al. assessed the 3-year clinical outcome of distal realignment and membrane-seeded ACI in selected patients with patellofemoral malalignment and large, isolated, patellar cartilage lesions [13]. The significant clinical improvement that they found support the value of associating distal realignment and ACI in treating large, isolated, patellar cartilage lesions associated with patellofemoral malalignment.

Gravius et al. evaluated whether or not osteochondral markers of the synovial fluid can be helpful in defining objectively the repair process following matrix-based autologous chondrocyte implantation (MACI) Cartilage Regeneration System (CaReS) [14]. Their conclusion was that specific markers for cartilage metabolism should be defined to permit a direct and objective comparison of the various conservative and operative methods presently available for the treatment of chondral lesions of the knee joint.

Nehrer et al. reported that although chondrocyte transplantation has been widely used with success, it has several inherent limitations, including its invasive nature and problems related to the use of the periosteal flap [15]. To overcome these problems chondrocyte transplantation combined with the use of biodegradable scaffolds was used. They used a hyaluronan-based scaffold (Hyalograft C), which compared favourably with classic chondrocyte transplantation. They stated that Hyalograft C is particularly indicated in younger patients with single lesions. The graft can be implanted through a miniarthrotomy and needs no additional fixation with sutures except optional fibrin gluing at the defect borders. Their results suggested that Hyalograft C is a valid alternative to chondrocyte transplantation.

### 1.2.4 Biological Methods

There are different biological approaches for the treatment of cartilage lesions: gene-activated matrices (GAM) from chitosan and gelatine, articular cartilage paste grafting technique, scaffolds, mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), growth factors (GFs), bone morphogenetic proteins (BMPs), magnetically labelled synovium-derived cells (M-SDCs), and elastic-like polypeptide gels, pulsed electromagnetic fields (PEMFs), and stem cell-coated titanium implants.

#### Gene-Activated Matrices (GAM) In Vitro

Guo et al. fabricated two- and three-dimensional matrices from chitosan and gelatin, then added a plasmid DNA encoding transforming growth factors- $\alpha$ 1 (TGF- $\alpha$ 1) for cartilage defect

regeneration [16]. First, they demonstrated that primary chondrocytes could maintain their biological characteristics and secrete therapeutic proteins when they were cultured onto gene-activated matrices (GAM) in vitro. Subsequently they inserted three-dimensional GAM into cartilage defects of rabbit knee joints. With the results of the new cartilage tissue formation, they came to the conclusion that GAM is helpful for new tissue production and this therapeutic protocol provided a cheap, simple, and effective method for cartilage defect reparation.

### Articular Cartilage Paste Grafting Technique

Stone et al. assessed clinical outcomes and regeneration of osteoarthritic cartilage lesions treated with an articular cartilage paste grafting technique [17]. The procedure offered excellent, long-lasting, pain relief, restored functioning, and possibility of tissue regeneration for patients with painful chondral lesions in both arthritic and traumatically injured knees.

### Scaffolds

Cartilage regeneration using a fibrin sponge and a stirring chamber was investigated by Shangkai et al. to improve the potential of articular cartilage tissue engineering [18]. Chondrocytes seeded on the fibroin-sponge scaffolds were cultured in the stirring chamber (a bioreactor facilitating mechanical stimulation) for up to 3 weeks. Changes in DNA content, glycosaminoglycan (GAG) amount, integrin subunits  $\alpha$ 5 and  $\beta$ 1 fluorescence intensity, and morphologic appearance, were studied to evaluate tissue maturity. Seeded scaffolds subjected to the stirring chamber demonstrated significant increases in both DNA content (38.9 %) and GAG content (54.3 %) at day 21 compared to the control group. In addition, the stirring chamber system facilitated a maturation of cartilage tissue showed by histologic examination, after a staining of proteoglycan and type II collagen. Clinical feasibility of the fibroin and stirring chamber system was evaluated using rabbit models with cartilage defect. Large defects on rabbit knee joints were repaired with

regenerated cartilage, which resembles hyaline cartilage at 12 weeks after operation. This study demonstrated the potential of such mechanically stimulated scaffold/cell constructs to support chondrogenesis *in vivo*.

Kon et al. evaluated the performance and the intrinsic stability of a newly developed biomimetic osteochondral scaffold and to test the safety and the feasibility of the surgical procedure [19]. A gradient composite osteochondral scaffold based on type I collagen-hydroxyapatite was obtained by nucleating collagen fibrils with hydroxyapatite nanoparticles. The technique was safe and MRI evaluation at short-term follow-up demonstrated good stability of the scaffold without any other fixation device. The preliminary clinical results at short-term follow-up were encouraging.

Chondral defects 4 mm in diameter (1 per sheep) were created by Jebel et al. in the centre of 1 medial femoral condyle of 48 sheep [20]. In the study twelve defects were allowed to heal spontaneously, 16 defects were covered with periosteal flaps alone, and 20 defects were filled with autologous *de novo* cartilage graft and overlaid with a periosteal flap. Chondral defects treated with *de novo* cartilage transplantation (NCT) show qualitatively better microscopic and macroscopic regeneration than do those treated with periosteal flaps alone. Results of the study showed that third-generation NCT is a promising development in the field of biologic cartilage regeneration.

The aim of the study of Swieszkowski was to show potential of using a tissue engineering approach for regeneration of osteochondral defects [21]. The study showed that in the field of cartilage repair or replacement, tissue engineering may have big impact in the future. *In vivo* bone and cartilage engineering via combining a novel composite, biphasic scaffold technology with MSCs has been shown a high potential in the knee defect regeneration in the animal models. However, the clinical application of tissue engineering requires the future research work due to several problems, such as scaffold design, cellular delivery and implantation strategies.

In an animal study performed by Chang et al., 15 miniature pigs were used in a randomised control study to compare tissue engineering with

allogeneous chondrocytes, autogeneos osteochondral transplantation, and spontaneous repair for osteochondral articular defects [22]. The results for the tissue engineering-treated group were satisfactory, the repair tissue being hyaline cartilage and/or fibrocartilage. Spontaneous healing and filling with scaffold alone did not result in good repair. With osteochondral defects, the subchondral bone plate was not restored by cartilage tissue engineering. These results showed that tri-copolymer can be used *in vivo* cartilage tissue engineering for the treatment of full-thickness articular defects.

Nugent et al. tested the hypothesis that bovine and human chondrocytes in a collagen type I scaffold will form hyaline cartilage *ex vivo* with immunohistochemical, biochemical, and magnetic resonance (MR) endpoints similar to the original native cartilage [23]. They concluded that the collagen-spot culture model supports formation and maturation of three-dimensional hyaline cartilage from active bovine chondrocytes.

### **Mesenchymal Stem Cells (MSCs)**

Agung et al. evaluated active mobilisation effect of MSCs into injured tissues after intraarticular injection of MSCs, and their contribution to tissue regeneration [24]. The study demonstrated the possibility of intraarticular injection of MSCs for the treatment of intraarticular tissue injuries including ACL, meniscus, or cartilage. If this treatment option is established, it can be minimally invasive compared to conventional surgeries for these tissues.

### **Platelet-Rich Plasma (PRP)**

PRP therapy is a simple, low cost and minimally invasive method that provides a natural concentrate of autologous blood growth factors (GFs) that can be used to enhance tissue regeneration. Filardo et al. investigated the persistence of the beneficial effects observed [25]. Their findings indicated that treatment with PRP injections can reduce pain and improve knee function and quality of life with short-term efficacy.

PRP is a natural concentrate of autologous blood growth factors experimented in different fields of medicine in order to test its potential to

enhance tissue regeneration. Kon et al. explored this novel approach to treat degenerative lesions of articular cartilage of the knee [26]. The preliminary results indicated that the treatment with PRP injections is safe and has the potential to reduce pain and improve knee function and quality of life in younger patients with low degree of articular degeneration.

### **Growth Factors**

Noh et al. evaluated cartilage regeneration in animal models involving induced knee joint damage [27]. Through cell-mediated gene therapy methods, a cell mixture comprising a 3:1 ratio of genetically unmodified human chondrocytes and transforming growth factor beta-1 (TGF-beta1)-secreting human chondrocytes (TG-C), generated via retroviral transduction, resulted in successful cartilage proliferation in damaged regions. The study demonstrated the safety and efficacy of TG-C following direct intra-articular administration in animal models involving induced knee joint damage. Based on these pre-clinical studies authorization has been received from the USA Food and Drug Administration (FDA) to proceed with an initial phase I clinical study of TG-C for degenerative arthritis.

### **Bone Morphogenetic Proteins (BMPs)**

Lavage fluids of knee joints of 47 patients were collected by Schmal et al. during surgical therapy [28]. Five patients had no cartilage lesion and served as a control group, the other 42 patients with circumscribed cartilage defects were treated by microfracturing or by an ACL. The concentrations of BMP-2 and BMP-7 were determined by ELISA. BMP-2 seemed to play an important role in surgically induced cartilage repair; synovial expression correlated with the clinical outcome.

### **Magnetically Labelled Synovium-Derived Cells (M-SDCs)**

Hori et al. investigated the chondrogenic potential of magnetically labelled synovium-derived cells (M-SDCs) and examined whether M-SDCs could repair the articular cartilage

using an intra-articular magnet after delivery to the lesion [29]. They demonstrated that articular cartilage defects could be repaired using an intra-articular magnet and M-SDCs. They believe that this system will be useful to repair human articular cartilage defects.

### **Elastic-Like Polypeptide Gels**

Nettles et al. evaluated an injectable, in situ crosslinkable elastin-like polypeptide (ELP) gel for application to cartilage matrix repair in critically sized defects in goat knees [30]. One cylindrical, osteochondral defect in each of seven animals was filled with an aqueous solution of ELP and a biocompatible, chemical crosslinker, while the contralateral defect remained unfilled and served as an internal control. At 3 months, ELP-filled defects scored significantly higher for integration by histological and gross grading compared to unfilled defects. ELP did not impede cell infiltration but appeared to be partly degraded. At 6 months, a new matrix in unfilled defects outpaced that in ELP-filled defects and scored significantly better for MRI evidence of adverse changes, as well as integration and proteoglycan-containing matrix via gross and histological grading. The ELP-crosslinker solution was easily delivered and formed stable, well-integrated gels that supported cell infiltration and matrix synthesis; however, rapid degradation suggested that ELP formulation modifications should be optimized for longer-term benefits in cartilage repair applications.

### **Pulsed Electromagnetic Fields (PEMFs)**

Zorzi et al. evaluated the effects of PEMFs in patients undergoing arthroscopic treatment of knee cartilage. Patients with knee pain were recruited and treated by arthroscopy with chondroabrasion and/or perforations and/or radiofrequencies [31]. Treatment with PEMFs aided patient recovery after arthroscopic surgery, reduced the use of NSAIDs, and also had a positive long-term effect.

### **Stem Cell-Coated Titanium Implants**

Frosch et al. evaluated the partial surface replacement of the knee with stem cell-coated

titanium implants and to provide a basis for a successful treatment of large osteochondral defects [32]. MSCs were isolated from bone marrow aspirates of adult sheep. Round titanium implants with a diameter of  $2 \times 7.3$  mm were seeded with autologous MSCs and inserted into an osteochondral defect in the medial femoral condyle. The results demonstrated that, in a significant number of cases, a partial joint resurfacing of the knee with stem cell-coated titanium implants occur. A slow bone and cartilage regeneration and an incomplete healing in half of the MSC-coated implants are limitations of the presented method.

### 1.2.5 Comparative Studies

Magnussen et al. asked whether ACI or osteochondral autograft transfer yields better clinical outcomes compared with one another or with traditional abrasive techniques for treatment of isolated articular cartilage defects and whether lesion size influences this clinical outcome [33]. The operative procedures included ACI, osteochondral autograft transfer, matrix-induced ACI, and microfracture. Minimum follow-up was 1 year (mean, 1.7 years). No technique consistently had superior results compared with the others. Outcomes for microfracture tended to be worse in larger lesions.

Saris et al. determined whether, in symptomatic cartilage defects of the femoral condyle, structural regeneration with characterised chondrocyte implantation is superior to repair with microfracture [34]. Both techniques were generally well tolerated; the incidence of adverse events after characterised chondrocyte implantation was not markedly increased compared with that for microfracture. One year after treatment, characterised chondrocyte implantation was associated with a tissue regenerate that was superior to that after microfracture. Short-term clinical outcome was similar for both treatments.

### 1.3 Osteotomies

Takeuchi et al. evaluated the clinical outcomes, in terms of early weight-bearing, of using

opening wedge high tibial osteotomy (OWHTO) to treat spontaneous osteonecrosis of the medial femoral condyle of the knee (SONK) using TomoFix and artificial bone substitute [35]. Damaged cartilage tissue was removed and drilling of the necrotic area followed by OWHTO was performed in 30 knees from 30 patients with an average age of 71 years at the time of operation. Patients were allowed to undertake partial weight-bearing exercises 1 week after the osteotomy procedure, with all patients performing full weight-bearing exercise at 2 weeks post-surgery. Necrotic area in each case was covered with fibrous cartilage-like tissue completely. Drilling of the necrotic area followed by OWHTO with TomoFix and artificial bone substitute was an effective treatment for SONK as it resulted in pain alleviation and regeneration of the fibrous cartilage tissue over the necrotic lesion.

Yercan et al. reported that excellent results of total knee arthroplasty have outweighed high tibial osteotomy applications in the treatment of osteoarthritis of the knee joint, but there is a growing interest in osteotomies as an adjunct in the treatment of full-thickness chondral and osteochondral lesions of the knee [36].

### 1.4 Meniscal Repair

Maher et al. assessed the performance of a degradable porous polyurethane scaffold in a partial meniscectomy ovine model [37]. The study showed that implantation of a polyurethane scaffold in a partial meniscectomy ovine model promotes tissue ingrowth without damaging the cartilage with which it articulates. Meniscal deficiency is a common occurrence, the effective clinical management of which is limited by the absence of an off-the-shelf implantable construct.

Recent all-inside meniscal repair devices are available, but in vivo studies with these devices are sparse. Hospodar et al. compared the FasT-Fix has inferior meniscal healing with the inside-out suture technique in the goat model. 73 male castrated goats (*Capra hircus*) underwent a 2-cm

meniscal incision and subsequent repair with the FasT-Fix device on one knee and inside-out meniscal repair on the contralateral knee [38]. Both repairs used a vertical mattress suture technique. Access to the menisci was via an open technique with an extra-articular osteotomy of the medial collateral ligament origin on the femur. The FasT-Fix meniscal repair had inferior meniscal healing results compared with the inside-out meniscal repair technique in the goat model.

Cook et al. reported that avascular meniscal tears are a common and costly problem for which current treatment options are limited [39]. A bioabsorbable conduit will allow for vascular tissue ingrowth that is associated with histologic and biomechanical evidence for avascular meniscal tear healing superior to that associated with meniscal trephining in dogs. Twenty five dogs underwent medial arthrotomy with creation of anterior and posterior tears in the medial menisci. The dogs were assigned treatments for their menisci: conduit or trephine. Conduit treatment resulted in functional healing with bridging tissue and biomechanical integrity in 71 % of avascular meniscal defects for up to 6 months after surgery. No functional healing was noted in avascular meniscal tears treated by trephination and suture repair. Clinical studies using the conduit in humans may be appropriate to determine the safety and efficacy of the device for cases of avascular and poorly vascularised meniscal tears, where the device can be successfully implanted from tear to meniscal rim, the tears can be surgically repaired, and patient compliance can be ensured.

To evaluate the influence of the chemical properties on the tissue regeneration in the implant, in the study of Tienen et al., the meniscus in the dog's knee was replaced with either an aromatic 4,4-diphenylmethanediisocyanate based polyesterurethane implant (Estane) or with an aliphatic 1,4-butanediisocyanate based polyesterurethane implant (PCLPU) [40]. The differences between these two implants did not seem to influence the tissue regeneration in the implant. However, PCLPU seemed to evoke less tissue reaction and, therefore, is thought to

be less or even nontoxic as compared with the Estane implant.

## 1.5 Other Related Topics

In this section a number of topics will be reviewed: specific healing response of cartilage lesions, cartilage healing in patellar fractures, the importance of surgical preparation, the prognostic factors involved and the assessment of results.

### 1.5.1 Specific Healing Response of Cartilage Lesions

Although many different interventions have been proposed for treating cartilage lesions at the time of anterior cruciate ligament (ACL) reconstruction, the normal healing response of these injuries has not been well documented. To address this point, Nakamura et al. compared the arthroscopic status of chondral lesions at the time of ACL reconstruction with that obtained at second-look arthroscopy [41]. The study revealed that there was a location-specific difference in the natural healing response of chondral injury. Untreated cartilage lesions on the femoral condyles had a superior healing response compared to those on the tibial plateau, and in the patellofemoral joint.

### 1.5.2 Cartilage Healing in Patellar Fractures

Anatomical open reduction is the choice treatment method in patellar fractures and the sole approach to study the cartilage surface healing is arthroscopy. Yavarikia et al. evaluated the cartilage healing, long after the complete union of the fractures and the long-term effects of simple transverse patellar fractures with perfect results on patellofemoral cartilage surface [42]. There was no relation between clinical signs and radiological characteristics of the patients with the healing on cartilage surface. Having a diagnostic arthroscopy in an appropriate time after fusion, especially during extracting the metal instrument, is effective on evaluating

patient's prognosis. Extracting metal instruments along with the simultaneous chondroplasty has low cost and complications, though leading to a decrease in the prevalence of secondary osteoarthritis and probably the eruptive swelling due to the debris released from probable fibrillations.

Gobbi et al. reported that tissue engineering has emerged as a potential therapeutic option for cartilage regeneration [43]. Hyaluronan-based scaffolds seeded with autologous chondrocytes are a viable treatment for damaged articular surface of the patellofemoral joint. Biodegradable scaffolds seeded with autologous chondrocytes can be a viable treatment for chondral lesions. The type of tissue repair achieved demonstrated histologic characteristics similar to normal articular cartilage.

### 1.5.3 Importance of Surgical Preparation

Mika et al. reported that to prevent haemorrhage, fibrin clot formation, and subsequent activation of the inflammatory response, surgical preparation for articular cartilage regeneration should avoid penetration of the subchondral bone plate [44]. Current surgical procedures with ring curettes do not violate the subchondral bone plate. Traditional debridement techniques for autologous chondrocyte implantation (ACI)/autologous chondrocyte transplantation (ACT) using a ring curette do not violate the normal subchondral bone plate in vitro or in vivo. Even in osteoarthritic knee joints, the bone plate is only violated by brute force.

Vizesi et al. compared the healing response of osteochondral defects created with either a punch or a drill in the weight-bearing region of the sheep knee at 4 and 26 weeks following surgery [45]. The use of a drill to create the defect creates a more aggressive inflammatory response at 4 weeks compared with a punch. However, by 26 weeks, defects created with a punch scored higher on a cartilage grading scale. Tissue damage at the time of surgery plays an important part in the sequence of events for healing of cartilage defects.

### 1.5.4 Prognostic Factors

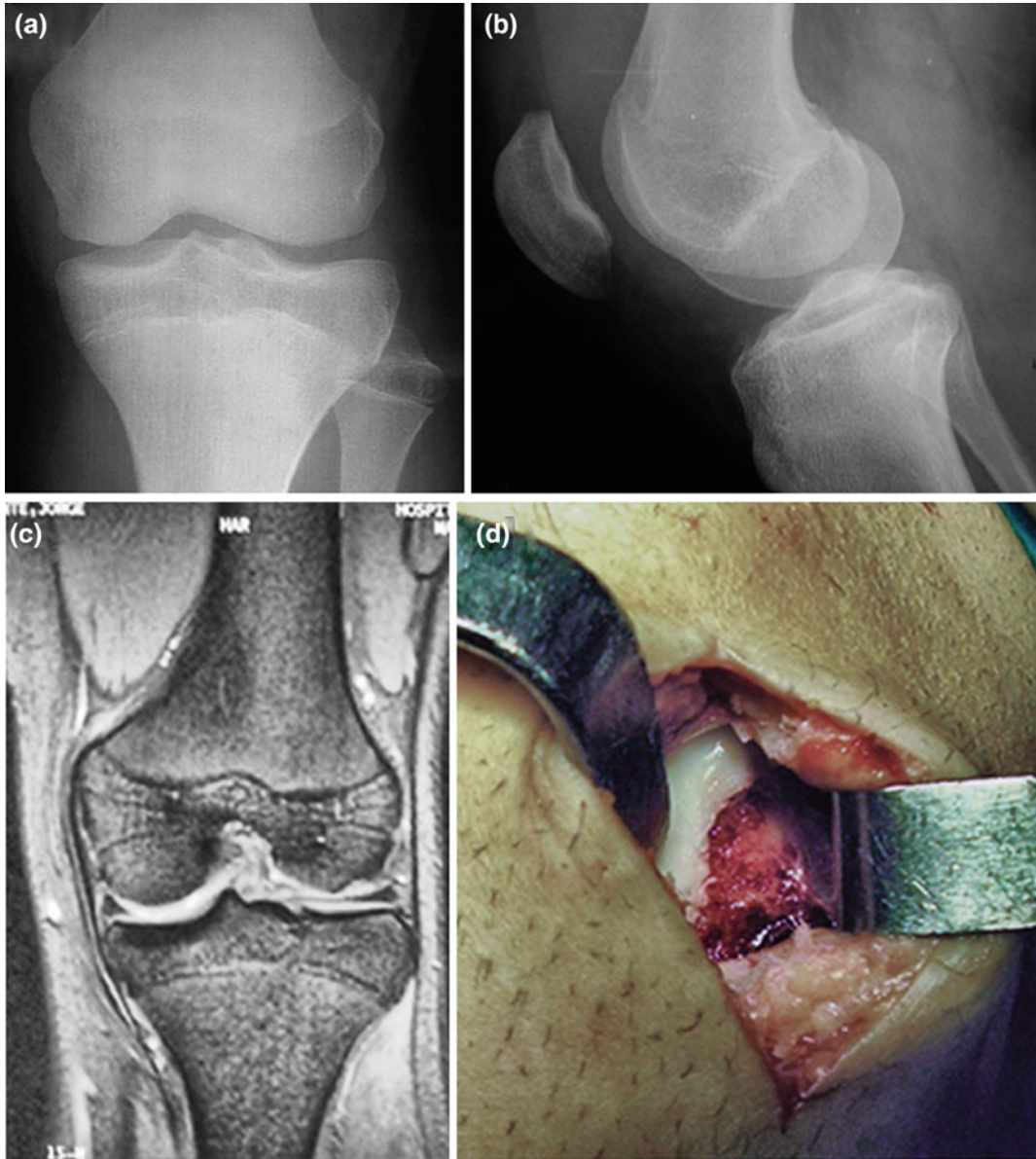
De Windt et al. analysed the prognostic value of patient age and defect size, age, and location on clinical outcome 3 years after cartilage therapy [5]. Defect size did not influence clinical improvement. Clinical outcome regarding the treatment of medial defects was better than that of the lateral defects. The improvement from baseline was better for patients  $\leq 30$  years compared with patients  $\geq 30$  years. The study illustrated the influence of patient age and defect location and age on clinical outcome 3 years after treatment of a focal cartilage lesion in patients with a traumatic knee injury.

### 1.5.5 Assessment of Results

Welsch et al. evaluated the potential of in vivo zonal T2-mapping as a non-invasive tool in the longitudinal visualisation of cartilage repair tissue maturation after MACI [46]. T2 mapping seems to be more sensitive in revealing changes in the repair tissue compared to morphological MR. In vivo zonal T2 assessment may be sensitive enough to characterise the maturation of cartilage repair tissue.

Gelse et al. reported that the increasing spectrum of different cartilage repair strategies requires the introduction of adequate non-destructive methods to analyse their outcome in vivo, i.e. arthroscopically [47]. The validity of non-destructive quantitative ultrasound biomicroscopy (UBM) was investigated in knee joints of five miniature pigs. The study confirmed that UBM can provide detailed imaging of articular cartilage and the subchondral bone interface also in repaired cartilage defects, and furthermore, contributes in certain aspects to a basal functional characterization of various forms of cartilage repair tissues. UBM could be further established to be applied arthroscopically in vivo.

Mamisch et al. determined on T2 cartilage maps the effect of unloading during a clinical MRI examination in the postoperative follow-up of patients after MACI of the knee joint [48]. The results suggested that T2 relaxation can be



**Fig. 1.2** Cartilage injury of the knee. **a** AP radiograph. **b** Lateral radiograph. **c** MRI (AP view). **d** Intraoperative view

used to assess early and late unloading values of articular cartilage in a clinical setting and that the time point of the quantitative T2 measurement affects the differentiation between native and abnormal articular cartilage.

Welsch et al. showed initial results of a multimodal approach using clinical scoring, morphological MRI and biochemical T2-

relaxation and diffusion-weighted imaging (DWI) in their ability to assess differences between cartilage repair tissue after microfracture therapy and MACI [49]. They concluded that in combination clinical, MRI-morphological and MRI-biochemical parameters can be seen as a promising multimodal tool in the follow-up of cartilage repair.

## 1.6 Discussion

Osteochondral articular defects are a key concern in orthopaedic surgery (Fig. 1.2). Current surgical techniques to repair osteochondral defects lead to poor subchondral bone regeneration and fibrocartilage formation, which is often associated with joint pain and stiffness [19, 26]. New cell-based treatments for articular cartilage repair are needed. As the optimal scaffold for cartilage repair has yet to be developed, scaffold-free cartilage implants may remove the complications caused by suboptimal scaffolds. The implantation of a scaffold-free, autologous de novo cartilage implant into standardised full-thickness cartilage defects of femoral condyles in sheep leads to a qualitatively better regenerative tissue than does periosteal flap alone or no treatment [20].

One matrix scaffold, a synthetic resorbable biphasic implant (TruFit Plug; Smith & Nephew, San Antonio, TX), seems to be a promising device for the treatment of osteochondral voids. The implant is intended to serve as a scaffold for native marrow elements and matrix ingrowth in chondral defect repair. The device is a resorbable tissue regeneration scaffold made predominantly from polylactide-co-glycolide copolymer, calcium sulfate, and polyglycolide. It is approved in Europe for the treatment of acute focal articular cartilage or osteochondral defects but is approved by the US Food and Drug Administration only for backfill of osteochondral autograft sites. Preclinical studies demonstrated restoration of hyaline-like cartilage in a goat model with subchondral bony incorporation at 12 months. Early clinical results of patients enrolled in the Hospital for Special Surgery Cartilage Registry have been favourable, with a good safety profile [50].

With regard to the current demographic changes in today's population and the increasing demands of the patients, i.e. in sports activity, the operative treatment of chondral lesions gained of importance in recent years [51]. The treatment of cartilage injuries is not only of great importance

in order to reduce the patients' symptoms, but also intends to avoid the appearance of secondary osteoarthritis. There are several different techniques available for the treatment of full-thickness defects (such as microfracture and ACI), some of them following related principles. The choice of the optimal treatment technique remains of great importance and represents one of the major responsibilities of the surgeon in order to achieve optimal results [51].

In order to obtain more robust and reproducible results, more detailed information is needed on many aspects including the fate of the cells, choice of cell type and culture parameters. As for the clinical aspects, it becomes clear that careful selection of patient groups is an important input parameter that should be optimised for each application. In addition, the study outcome parameters should be improved. Although reduced pain and improved function are, from the patient's perspective, the most important outcomes, there is a need for more structure/tissue-related outcome measures. Ideally, criteria and/or markers to identify patients at risk and responders to treatment are the ultimate goal for these more sophisticated regenerative approaches in joint surface repair in particular, and regenerative medicine in general [7].

There are challenges in translation from animals to humans as anatomy and structures are different and immobilisation to protect delicate repairs can be difficult. The tissues potentially generated by proposed cartilage repair strategies must be compared with the spontaneous changes that occur in similarly created untreated lesions. The prevention of the secondary changes in the surrounding cartilage and subchondral bone described in this article should be addressed with the introduction of treatments for repairs of the articulating surface [8].

Trends in science are beginning to suggest that cartilage degeneration may be related to a chronic imbalance in extracellular matrix metabolism. In cartilage, a combination of biomechanical, biochemical, and matrix-related signalling pathways regulates the equilibrium

between cartilage anabolism and catabolism. A potential limitation of many current treatments of osteoarthritis is that they may not comprehensively restore regulation of a balance between cartilage anabolism and catabolism [52].

The social impact of bone and cartilage pathologies entails high costs in terms of therapeutic treatments and loss of income. As a result, the current research trend includes preventive interventions and therapeutic solutions that can lead to an enhancement of tissue regeneration and the reduction of degenerative mechanisms. Many options have been made available to address problems regarding cartilage damage, each with its own advantages and disadvantages. Several studies are currently in progress to clarify some of the questions that remain unanswered about the long-term durability of these procedures and the possible modifications that can be made to achieve better results. Biotechnology is progressing at a rapid pace that allows the introductions of several products for clinical application; however, randomised, prospective studies for these innovations should be conducted to validate the safety and efficacy of cartilage regeneration [53].

The newest, third-generation techniques have been developed to address the limitations of earlier techniques. These new procedures use 3 novel approaches: chondro-inductive or chondro-conductive matrix; use of allogeneic cells, both of which may allow a single-stage surgical approach; and techniques to mechanically condition the developing tissue before surgical application to improve the material properties and maturation of the implant. However, at this time there is very limited clinical data available on the nature and outcomes of these procedures [54].

Severe joint inflammation following trauma, arthroscopic surgery or infection can damage articular cartilage, thus every effort should be made to protect cartilage from the catabolic effects of pro-inflammatory cytokines and stimulate cartilage anabolic activities. PEMFs can protect articular cartilage from the catabolic effects of pro-inflammatory cytokines, and

prevent its degeneration, finally resulting in chondroprotection [31].

A cartilage defect has a very limited ability to repair itself spontaneously due to the shortage of blood. Many attempts have been made to restore the integrity of cartilage in clinical and experimental studies. Recently, tissue engineering has emerged as a new protocol for lost tissue regeneration. Meanwhile, the defect-repairing environment can be improved by gene therapy methods. Gene-activated matrices (GAMs) fabricated with biomaterials and plasmids fill the cartilage defects to restore the integrity of joint surface, facilitating repair cell adhesion and proliferation as well as the synthesis of extracellular matrix. And they also serve as a local gene delivery system, inducing therapeutic agent expression at the repair site [16].

Cartilage has an extremely poor capacity to heal, which has led to intensive research into biomaterials and tissue engineering for the purpose of regenerating cartilage *in vivo*. Many of these techniques have shown great promise *in vitro*; however, the results do not always carry across to the *in vivo* scenario. Healthy cartilage autografts often do not integrate with the adjacent cartilage, suggesting that cartilage is rarely capable of healing even under ideal conditions [45].

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## 1.7 Conclusions

The treatment of cartilage injuries is not only of great importance in order to reduce the patients' symptoms, but also intends to avoid the appearance of secondary osteoarthritis. There are several different techniques available for the treatment of full-thickness defects (such as microfracture and ACI), some of them following related principles. The choice of the optimal treatment technique remains of great importance and represents one of the major responsibilities of the surgeon in order to achieve optimal results. The creation of cartilage repair tissue relies on the implantation or neosynthesis of cartilage matrix elements. One cartilage repair

strategy involves the implantation of bioabsorbable matrices that immediately fill a chondral or osteochondral defect. Such matrices support the local migration of chondrogenic or osteogenic cells that ultimately synthesize new ground substance. The goal of all cartilage replacement techniques is the reformation of mature organised hyaline cartilage. However, currently cartilage repair techniques lead principally to production of fibrocartilage, which has material properties that are inferior to hyaline cartilage. Cell-based therapies such as ACI hold promise for cartilage regeneration; however, these techniques still do not predictably result in hyaline cartilage formation.

ACI, osteochondral autograft transplantation (mosaicplasty), matrix-induced ACI (MACI), and microfracture have shown similar results. Clinical outcome regarding the treatment of medial defects is better than that of the lateral defects. The improvement from baseline is better for patients  $\leq 30$  years compared with patients  $\geq 30$  years. Some biological methods such as scaffolds, MSCs, GF, M-SDCs, BMPs and elastic-like polypeptide gels, still need more research. Meniscal repair also needs further development.

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