Cell-Based Cartilage Regeneration

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Abstract

Since decades various regenerative cell-based treatment options have been developed for cartilage repair. With the introduction of the autologous chondrocyte transplantation, also large-sized chondral defects can be successfully addressed. This chapter gives a short overview about current procedures for cell-based treatment strategies like bone marrow stimulation techniques, osteochondral transplantation, and chondrocyte transplantation. Requirements and outcome parameters for a successful treatment and future directions in cartilage regeneration are discussed. Finally treatment recommendations according to cartilage defect size and depth are given.

5.1 Introduction

Articular cartilage injuries are common. They can result from acute traumatic injuries, posttraumatic or early degenerative changes, osteochondritis dissecans, or avascular necrosis. Numerous reports analyzing high numbers of arthroscopies show cartilage lesions in up to 60% of the patients (Widuchowski et al. 2007). The incidence of chondral injuries indicates the high impact on the society, as it is

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generally agreed that the persistence of cartilage defects is a risk factor for joint dysfunction, which finally may lead to severe osteoarthritis.

Cartilage lesions can remain symptomless over a long period of time. This can cause a delayed diagnosis and late treatment of cartilage injuries, which may have negative consequences for joint recovery. Clearly, this emphasizes the importance of an adequate regenerative treatment of cartilage lesions at the earliest time point in order to prevent onset and development of osteoarthritis (Zellner et al. 2015).

Since decades regenerative treatment options for small- and middle-sized cartilage lesions were developed like, e.g., Pridie drilling or microfracture. With the introduction of the "autologous chondrocyte transplantation (ACT)" technique by Brittberg et al. in 1994, also large-sized cartilage defects can be successfully addressed via a regenerative approach (Brittberg et al. 1994).

Recently many randomized clinical trials investigated the efficiency and the quality of different cartilage repair procedures. Most of them enrolled young and active patients with "ideal" chondral defects that were focal and isolated with clearly defined borders (Lattermann and Luckett 2011). However, in reality, most patients that present with clinically symptomatic chondral lesions do not fulfill these criteria. Consecutively a detailed analysis and assessment of the cartilage defect and all underlying pathologies should be performed. Specific comorbidities have to be taken into account prior to performing regenerative cartilage repair as they may require additional concomitant or staged surgical procedures.

All cell-based cartilage repair strategies like bone marrow stimulating techniques or autologous chondrocyte transplantation require a correction of the comorbidities like malalignment, meniscal deficiency, instability, or pathologies of the subchondral bone. Only if the comorbidities are addressed sufficiently, the chance for appropriate cartilage regeneration is achievable.

Axis deviations can cause overload of an affected joint compartment. For cartilage treatment, malalignment needs be corrected to restore normal load distribution that allows the repair tissue to adjust to physiological loads. Corrected patellofemoral and tibiofemoral alignment improves clinical outcome when realignment operations are performed concurrently with the cartilage repair or as a staged procedure (Behery et al. 2014).

Another factor contributing to successful cartilage regeneration is the meniscal status. As the menisci are critical for shock absorption and load distribution in the knee joint, meniscal deficiency also affects cartilage regeneration (Makris et al. 2011). Meniscal lesions should be treated adequately in combination with cartilage regeneration. Because of the direct correlation between the lost amount of meniscus tissue and the increase of load on the surrounding cartilage, as much meniscus substance as possible should be restored (McDermott and Amis 2006) which can be achieved by suturing or limited partial resection. In case of previous subtotal meniscectomy, also meniscal supplementation or allograft transplantation should be discussed in order to restore a normal joint physiology for cartilage regeneration.

It has been clearly shown that joint instability contributes to a significant increase in cartilage lesions. In the long term, ACL insufficiency is a negative predictor for development of knee osteoarthritis. Therefore the correction of ligamentous

instability by ligament reconstruction is a mandatory requirement for regenerative cartilage treatment.

Besides the alignment, meniscal integrity, and knee stability, the status of the subchondral bone is crucial for a successful cartilage repair. It has been shown that the adjacent bone quality affects the regeneration of the cartilage defect (Gomoll et al. 2010). So the state of the subchondral bone needs also to be taken into account for planning a regenerative cartilage repair procedure.

In conclusion, analysis, evaluation, and correction of all comorbidities and underlying pathologies are mandatory requirements for a good clinical outcome after cell-based cartilage regeneration procedures.

5.2 Regenerative Treatment Options for Cartilage Repair

5.2.1 Bone Marrow Stimulation Techniques

Due to their simplicity and low costs, bone marrow stimulation techniques are the most commonly used procedures among regenerative options for cartilage treatment worldwide. Developed by Steadman in the 1980s as an enhancement of tissue response techniques like drilling (Pridie) and abrasion arthroplasty (Johnson), this widely used procedure is generally regarded as safe and effective. Cartilage repair with the microfracture technique involves several systematic steps, including debridement to a stable cartilage margin creating a stable defect containment, careful removal of the calcified cartilage layer with special curettes or shavers, and homogeneous microfracture penetrations within the cartilage defect with specific awls perpendicular to the subchondral bone plate. This procedure results in a complete defect filling by a well-anchored mesenchymal clot (Mithoefer et al. 2009b) (Fig. 5.1).

The aim is to recruit bone marrow cells via creating a communication between cartilage lesions and subchondral bone to get access to potential cartilage precursor cells. Stem cells migrate from the marrow cavity to the fibrin clot of the defect and promote the formation of a fibrocartilaginous tissue (Marcacci et al. 2013). Arthroscopically performed microfracturing is a cost-saving procedure with a low complication rate and mainly successful for small defects. However the development of tissue hypertrophy or formation of soft scar tissue that lacks the mechanical characteristics of hyaline cartilage are disadvantages of this specific treatment (Fortier et al. 2012).

According to the recent literature, good indications for treatment of chondral lesions with microfracture are:

- Small defect size (<3 cm^2)
- Full-thickness, traumatic cartilage defects (Outerbridge grades III and IV) with full containment
- Intact articulating joint surface
- Patient age between 18 and 50 years

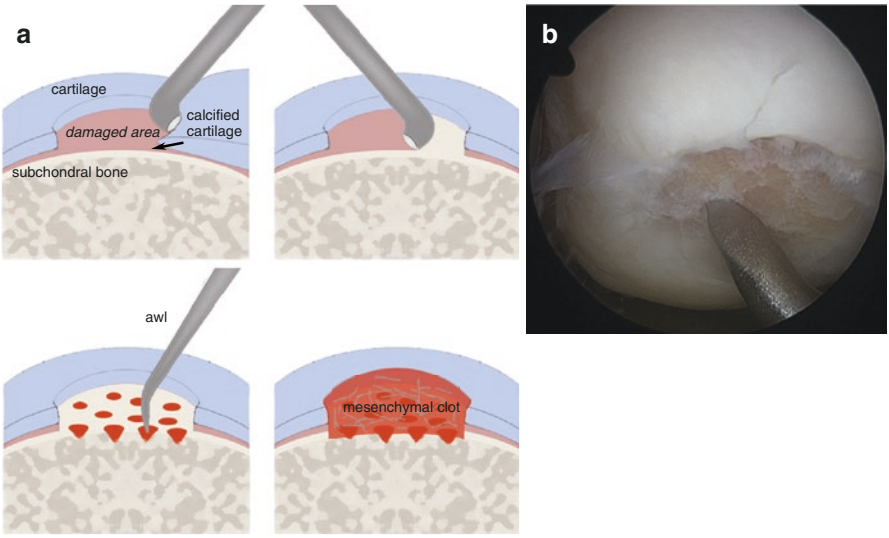

Fig 5.1 (**a**) Schematic drawing of cartilage repair using the microfracture technique. After debridement in order to create stable defect edges (*upper left*), the calcified cartilage layer is removed (*upper right*), and microfracture penetrations are placed in the defect with a distance of 3–4 mm (*lower left*), resulting in defect filling with a mesenchymal clot (*lower right*) (adopted from Mithoefer et al. 2009b). (**b**) Arthroscopic view of a microfracture procedure for treatment of a full-size cartilage defect at the lateral femoral condyle after preparation of stable defect edges (containment)

- No or corrected concomitant morbidity (axis deviation, instability, meniscus injuries, subchondral bone pathology)
- Full range of motion of the affected joint

An important factor for a successful outcome after microfracture treatment seems to be the postoperative rehabilitation protocol. Partial weight bearing with no more than 20 kg and the use of CPM is recommended for 6 weeks without limitation of the range of motion (Steadman et al. 2001).

In a systematic review, Mithoefer et al. (2009b) observed that microfracturing provides effective functional improvement for at least 2 years. In smaller defects, microfracture shows promising results concerning mobility, reduction of pain, and return to sport (Kon et al. 2011). Positive prognostic factors for a successful cartilage treatment with microfracture are size smaller than 3 cm^2, BMI less than 30 kg/m^2, femoral defects, age younger than 40, interval of pain less than 1 year, and no previous knee surgery. However, recent reports show that over time the results of microfracture are getting worse especially in active patients and larger chondral defects 5 years after the procedure. Additionally, the effects of microfracture are patient age related, meaning that older patients do not seem to profit at the same extent from this specific treatment as compared to young patients (Kreuz et al. 2006; Mithoefer et al. 2009a). The repair tissue response is often unpredictable; fibrous, soft, spongiform tissue combined with central degeneration is frequently found, and

patients may have to adjust their activity level to that of their knee function (Nehrer et al. 1999). Another reason for the deterioration of the clinical outcome after microfracture over time might be the development of subchondral sclerosis and cysts or the formation of intralesional osteophytes. Consecutively a complication rate of up to 50% after microfracturing is described in literature after 5 years. Recent results published in the literature recommend using these procedures only for the treatment of acute and small lesions and not in large cartilage defects anymore.

Further developments in the field of bone marrow stimulating techniques try to overcome the shortcomings of the procedures. In combination with the microfracture technique, coverage of the prepared and treated chondral defect site by a biomaterial is becoming more and more popular. This enhanced procedure was first described by Gille et al. (2010). The so-called autologous matrix-induced chondrogenesis (AMIC) reveals promising results in terms of functional outcome. In a prospective study, Gille et al. investigated 27 patients up to 62 months with a mean defect size of 4.2 cm^2. 87% of the patients showed an increase in functional outcome scores like ICRS, Tegner, Cincinnati et al. compared to the preoperative status. In another study, the same authors detected a significant decrease of pain in the VAS after 1 and 2 years postoperatively (Gille et al. 2013). Kusano et al. (2012) also detected significant improvements in functional scores and pain reduction after 29 months, but MRI findings showed generally incomplete or inhomogeneous tissue filling. Comparing AMIC with the original microfracturing technique, Anders et al. (2013) found no significant differences in the IKDC or Cincinnati score at 1- or 2-year follow-ups. A recent study has shown an improvement in repair tissue quality by enhancing microfracture with a chitosan-based biomaterial (BST-CarGel; Piramal, Laval, Quebec, Canada) (Stanish et al. 2013). Mixed with autologous blood, it stabilizes the clot and enhances marrow-derived repair in the microfractured cartilage lesion. Using this technique, Stanish et al. observed an equivalent clinical benefit compared to microfracturing alone, but a greater defect filling and superior repair tissue quality in MRI evaluation. Further studies and long-term results will show whether enhanced microfracture techniques are really capable to overcome the shortcomings of the original procedure regarding the development of intralesional osteophytes or formation of subchondral cysts. However, there is doubt whether these modifications make microfracture-based techniques more appropriate for treatment of large-sized chondral defects.

Recently the technique of microfracturing has been modified to a microdrilling method. The idea of drilling holes through the damaged cartilage area into the subchondral bone marrow space to stimulate repair tissue was first described by Pridie. Thermal necrosis was a potential disadvantage that could affect the outcome. The improved modern microdrilling version with arthroscopically applicable narrow-caliber drills up to 4 mm in depth is more reproducible and less traumatic. In an animal model, Chen et al. compared this “micro-Pridie” drilling method histologically with standard microfracturing. While microfracture caused compacted bone formation around the created holes that sealed them off from viable bone marrow, drilling cleanly removed the bone from the holes and provided access channels to marrow stroma. Heat necrosis was not seen in the drilling group (Chen et al. 2009).

Furthermore Eldracher et al. demonstrated improved osteochondral repair by application of smaller drill holes that reflect the physiological trabecular distance in a translational sheep model. They conclude to use small-diameter bone-cutting devices for subchondral drilling (Eldracher et al. 2014). However, no prospective clinical trial has shown significant improvement of the microdrilling method over the original microfracture technique yet.

5.2.2 Autologous Osteochondral Transplantation

Focal (osteo-)chondral defects may also be addressed with osteochondral autograft transplantation (OAT). It is the only method to transfer native hyaline articular cartilage into the defect area. Harvesting and subsequent implantation of autologous osteochondral plugs is performed in a one-step procedure. The plugs are frequently taken via a small incision from a non-weight-bearing area such as the medial or lateral margin of the trochlea or the intercondylar notch. This procedure guarantees a tissue transfer of viable osteochondral units that aims to integrate via bone-to-bone healing, since the mature cartilage tissue has limited healing potential and rarely fully heals and integrates with surrounding cartilage. The fast bone-to-bone integration allows a rehab program with a rapid increase in weight bearing. In the early 1990s, Hangody conceived and perfected the mosaicplasty technique, which uses multiple small-diameter osteochondral plugs that can be implanted also through an arthroscopic approach, and good results have been reported at long-term follow-up, particularly for defects up to 4 cm^2 (Hangody et al. 2010). Especially deep focal chondral defects which affect the subchondral plate or small cartilage lesions with pathologies of the subchondral bone like cysts may be responsive to a treatment with OAT. In controlled randomized prospective studies, Gudas et al. (2012) showed significantly better clinical results after 12, 24, and 36 months comparing OAT versus microfracture. Compared to other regenerative treatment options, OAT requires the shortest postoperative time of partial weight bearing during the rehabilitation period. Consecutively, time to return to sport is diminished. However, with increasing defect size, complication rate rises due to integration problems and donor site morbidity. Therefore, treatment of chondral defects larger than 3–4 cm^2 with OAT is no longer recommended in literature.

5.2.3 Autologous Chondrocyte Transplantation

The treatment of choice for large full-thickness articular cartilage defects is the matrix-guided autologous chondrocyte transplantation (MACT).

Brittberg et al. (1994) first introduced the technique of the autologous chondrocyte transplantation (ACT) in 1994. Particularly for treatment of cartilage defects larger than 3 cm^2, the ACT method revealed superior long-term success (Bentley et al. 2012). The conventional technique is accompanied with periosteum harvest and fixation over the cartilage defects via large skin incisions. Autologous

chondrocytes were injected underneath the periosteal flap. Hypertrophy of the periosteum with high rate of revision arthroscopies and the risk of transplant failure of up to 20% were major drawbacks of the conventional autologous chondrocyte transplantation technique.

MACT was developed to address these problems. In a first arthroscopy, small osteochondral plugs are taken from the non-weight-bearing cartilage adjacent to the lateral femoral notch. Then the chondrocytes are isolated, cultured, and seeded on biodegradable scaffolds. Approximately 3 weeks after the first arthroscopy, the cell-seeded scaffolds are implanted into cartilage defects. Therefore, the lesion is prepared by removal of the calcified cartilage layer and creation of containment with stable rims of the defect. The cell-matrix construct is then fixed in the defect with sutures or biodegradable devices like plugs or anchors (Fig. 5.2).

Another technique uses self-adhering chondrospheres to fill the defect. These further developments of the ACT technique enable to minimize the incision and to perform the procedure in a "mini-open" way or arthroscopically. Consecutively the rehabilitation time was reduced and the complication rate diminished.

With the new MACT technique, also some other disadvantages of the ACT were eliminated (Harris et al. 2011). The rate of hypertrophy of the transplant that may be caused by the biologically active periosteal flap was reduced by the matrix-guided technique.

An advantage of the second and third generation of the autologous chondrocyte transplantation is the scaffold-based technique that also simplified the surgical procedure. The biomaterial represents a temporary 3D structure of biodegradable

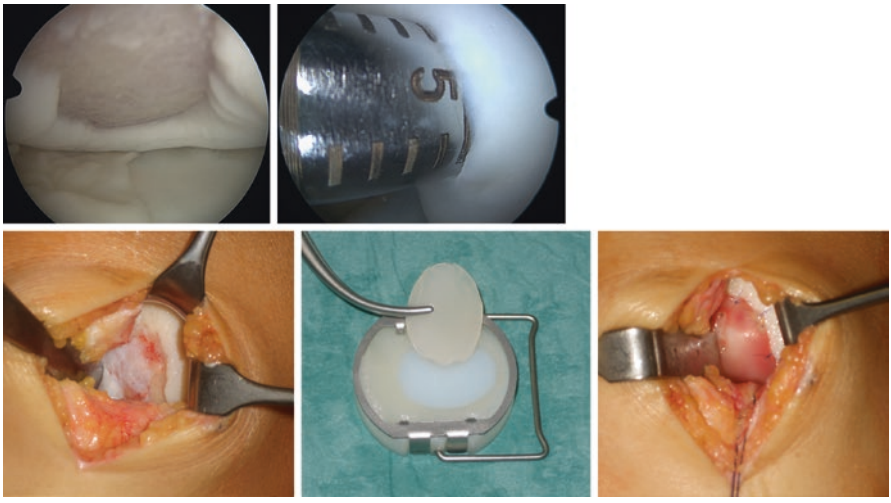

Fig. 5.2 *Upper row*: arthroscopic evaluation of a full-size cartilage defect at the lateral femoral condyle and harvesting of osteochondral plugs from the medial edge of the lateral notch border for further culture of autologous chondrocytes. *Lower row*: 3 weeks after cell harvest, the defect at the lateral femoral condyle is prepared via mini-arthrotomy. After cutting the autologous chondrocyte transplant to the correct size, the cell-seeded implant is placed into the defect and fixed with sutures

polymers, which favors the growth of the specific cartilaginous cell type. An ideal scaffold should mimic the biological and structural properties of native cartilage in order to enable cell infiltration, attachment, proliferation, and differentiation. The matrix should be biocompatible and biodegradable in order to support initial tissue formation and then to be gradually replaced by the regenerated tissue. The different three-dimensional biomaterials support the redifferentiation process, cell protection in the initial phase, and a homogenous cell distribution in the defect.

Compared to other reconstructive therapy options for cartilage defects like microfracturing, MACT restores the cartilage defect up to date with the best quality of the regenerated tissue (Vavken and Samartzis 2010).

Especially for full-thickness cartilage defects larger than 4 cm^2, MACT is the recommended therapy in literature (Niemeyer et al. 2016). Other cartilage therapy procedures failed to improve the clinical outcome of cartilage defects of that size.

In a controlled randomized prospective study for large-sized chondral defects (4–10 cm^2), the outcome after MACT was significantly better after 2 years compared to microfracture (Basad et al. 2010). Similar long-term results were seen for active patients comparing MACT with microfracture. In another randomized prospective study, Crawford et al. saw significantly more therapy responder in the MACT group compared to the microfracture group after 6, 12, or 24 months. These results correlated to the clinical and functional outcome of the patients in the KOOS and IKDC scores (Crawford et al. 2012).

The reason for the superior results after MACT compared to microfracture might be the better defect filling, the histological results, and the lack of osteophytes in the defect site or the regenerated tissue, which can be predominantly detected 4 or 5 years after microfracture (Zellner et al. 2015).

However, if microfracture fails as primary procedure for treatment of a chondral defect, the risk of treatment failure after the secondary performed MACT increases significantly. For that reason some authors do not recommend microfracture as a first-line treatment especially for larger defects. On the other hand, there are reports in literature, which reveal good results of MACT even as a second-line therapy procedure. Additionally the age-related effects of a cartilage therapy seem to be less significant with MACT in comparison to microfracture.

In a controlled randomized prospective study, Bentley et al. (2012) showed significantly better outcome results after ACI compared to OAT. The best clinical results of MACT were observed for traumatic chondral lesions and for osteochondrosis dissecans. On the other hand, degenerative cartilage defects and chronic lesions are still difficult to treat, especially when patients with a long history of pain show a significantly worse outcome after MACT (Angele et al. 2015).

In a published study, Vanlauwe et al. compared ACI with microfracture and showed a significant improvement of patients' outcome after MACT when the symptoms of the cartilage lesion did not last more than 3 years. On the other hand, in patients with clinical symptoms more than 3 years, ACI failed to improve the functional outcome significantly compared to microfracture (Vanlauwe et al. 2011).

The earlier a biological cartilage repair is performed, the better are the clinical results. Consecutively primary cartilage defects should be treated as soon as possible to improve the long-term outcome.

Another problem for biological cartilage repair is the localization of the defect. Results of all treatment options behind the patella are worse than in other parts of the knee joint (Niemeyer et al. 2011). Also in the original description of the ACI technique, Brittberg et al. observed significant more treatment failures for defects in the patellofemoral compartment. Probably the special biomechanical situation in the retropatellar area is the reason for the higher rate of cartilage treatment failure. As this is not a problem of a specific cartilage repair procedure, the necessity arises to address all pathologies for a successful cartilage treatment behind the patella. Comparable to malalignment of the leg axis, knee instability, or meniscal tears in the femorotibial compartment, all pathologies like maltracking of the patella or dysplasia in the retropatellar area should be corrected.

As mentioned above the status of the subchondral bone is crucial for successful cartilage regeneration. For deep osteochondral defects like in osteochondritis dissecans, the MACT can be combined with bone augmentation like cancellous bone grafting or autologous bone transplantation, e.g., from the iliac crest. After reconstruction of the osseous part, the defect is covered by MACT.

Macroscopic and histological findings play an important role after MACT. For the evaluation of the quality of the regenerated tissue, not only histological findings but also the amount of defect filling, the surface quality, and the integration into the surrounding native cartilage are important (Nehrer et al. 1999).

It has been shown that complete defect filling with differentiated tissue correlates with good clinical results. On the other hand, incomplete defect filling with undifferentiated scar tissue reveals unsatisfying scoring results with ongoing pain and worse joint function of the patients (Henderson et al. 2007). This effect can be particularly seen in larger chondral defects. In a pilot study, we reported that the transplant quality is adequate at the time of surgery of MACT. We retrospectively reviewed 125 patients with large localized cartilage defects (mean defect size 5 cm^2) of the knee who were treated with MACT. Portions of the cell-matrix constructs that were not implanted in the cartilage defects were further cultured and tested for their potential to form articular cartilage. In vitro assessment of the cell-matrix implants showed chondrogenic differentiation with positive staining for glycosaminoglycans and collagen II in all cultures. Enzyme-linked immunosorbent assay confirmed an increase of collagen II production. Clinically, we observed an improvement in median IKDC score from 41 to 67 points at the last follow-up indicating that cartilage extracellular matrix deposition shows adequate implant quality for MACT at the time of implantation and justifies the use for treatment of large cartilage defects (Zellner et al. 2013).

Besides regulatory restrictions and high costs, a disadvantage of today's autologous chondrocyte transplantation is the necessity of two steps for the surgical procedure. After cell harvest a certain time of cultivation and expansion of the chondrocytes is mandatory prior to the application. Consecutively, the patient needs two operations plus the phenotype and quality of the transplanted chondrocytes

might be affected. Future directions are aiming for the development of one-step procedures.

Appropriate cell types might help to affect the complexity of ACI and simplify surgical procedures. Alternative cell sources are allogenic cells or mesenchymal stem cells. Allogenic chondrocytes can help to reduce donor site morbidity. In combination with a biocompatible and chondroinductive matrix, allogenic chondrocytes harvested from neonatal donors or from donor's knee joints within 24 h of death may be used in a single-stage procedure (Farr et al. 2014). Preliminary results demonstrated a safe and effective treatment for cartilage defects with a mean lesion size of 2.7 cm^2. Clinical outcomes showed significant improvement over baseline and favorable histological repair tissue 2 years postoperatively. Dhollander et al. reported of midterm results after implantation of alginate beads containing human mature allogenic chondrocytes in cartilage lesions of the knee. Twenty-one patients were followed for an average period of 6.3 years, and a significant improvement in WOMAC and VAS scores was observed. However, four failures occurred and MRI evaluation with the MOCART score only revealed moderate values (Dhollander et al. 2012).

Autologous adult mesenchymal stem cells (MSCs) are a potential cell source for a single-step cell-based treatment of large cartilage defects. MSCs have a better proliferation rate than chondrocytes and a high potential for differentiation into several lineages including chondrogenesis. Autologous MSCs can derive from many sources. Particularly, bone marrow-derived MSCs (BMSCs) combine many advantages as they are easy to isolate and to store. Extensive preclinical and clinical work has shown that BMSCs can differentiate into cartilage among other tissues. Other potential sources for MSCs are adipose tissue, muscle, synovium, periosteum, and umbilical cord. Nejadnik et al. (2010) analyzed the clinical outcome of patients treated with autologous BMSCs compared to patients treated with first-generation ACI for large cartilage defects in the knee. After 2 years a similar functional outcome regarding IKDC, Lysholm, or Tegner scores was found. The authors concluded that using BMSCs for articular cartilage repair is as effective as chondrocytes. In addition, it required one less knee surgery, reduced costs, and minimized donor site morbidity. However, in some countries, regulatory burdens might be a problem for implementing the use of autologous mesenchymal stem cells into daily clinical practice.

5.2.4 Current Treatment Recommendations for Chondral Injuries

In their current review, Niemeyer et al. (2016) provide a concise overview on important scientific background issues and the results of clinical studies discussing advantages and disadvantages of ACI and other cartilage treatment options. They describe the biology and function of healthy articular cartilage, the present state of knowledge concerning potential consequences of primary cartilage lesions, and the suitable indication for ACI. Based on current evidence, an indication for ACI is given

for symptomatic cartilage defects starting from defect sizes of more than 3–4 cm^2 in the case of young and active sports patients at 2.5 cm^2. Smaller lesions are supposed to be treated by bone marrow stimulating techniques like microfracturing. However, the status of the subchondral bone will influence the decision-making process for cartilage therapy. Smaller defects with pathologies of the whole osteochondral unit are best treated with OAT. For large and deep osteochondral lesions, a combination of MACT and bone augmentation techniques is the favorable treatment option.

Conclusions

With increasing knowledge cell-based cartilage regeneration becomes a more and more routinely used technique with well-predictable outcome and results. As research activities are increasing in the field of regenerative joint therapy, recent developments help to overcome remaining limitations step by step. Simplification of regulatory burdens is needed to transfer rising knowledge and developments into daily clinical practice.

References

Anders S, Volz M, Frick H, Gellissen J (2013) A randomized, controlled trial comparing autologous matrix-induced chondrogenesis (AMIC(R)) to microfracture: analysis of 1- and 2-year follow-up data of 2 centers. Open Orthop J 7:133–143. doi:10.2174/1874325001307010133

Angele P, Fritz J, Albrecht D, Koh J, Zellner J (2015) Defect type, localization and marker gene expression determines early adverse events of matrix-associated autologous chondrocyte implantation. Injury 46(Suppl 4):S2–S9. doi:10.1016/S0020-1383(15)30012-7

Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J (2010) Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 18(4):519–527. doi:10.1007/s00167-009-1028-1

Behery O, Siston RA, Harris JD, Flanigan DC (2014) Treatment of cartilage defects of the knee: expanding on the existing algorithm. Clin J Sport Med 24(1):21–30. doi:10.1097/JSM.0000000000000004

Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RW (2012) Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. J Bone Joint Surg 94(4):504–509. doi:10.1302/0301-620X.94B4.27495

Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331(14):889–895. doi:10.1056/NEJM199410063311401

Chen H, Sun J, Hoemann CD, Lascau-Coman V, Ouyang W, McKee MD, Shive MS, Buschmann MD (2009) Drilling and microfracture lead to different bone structure and necrosis during bone-marrow stimulation for cartilage repair. J Orthop Res 27(11):1432–1438. doi:10.1002/jor.20905

Crawford DC, DeBerardino TM, Williams RJ 3rd (2012) NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. J Bone Joint Surg Am 94(11):979–989. doi:10.2106/JBJS.K.00533

Dhollander AA, Verdonk PC, Lambrecht S, Verdonk R, Elewaut D, Verbruggen G, Almqvist KF (2012) Midterm results of the treatment of cartilage defects in the knee using alginate beads containing human mature allogenic chondrocytes. Am J Sports Med 40(1):75–82. doi:10.1177/0363546511423013

Eldracher M, Orth P, Cucchiarini M, Pape D, Madry H (2014) Small subchondral drill holes improve marrow stimulation of articular cartilage defects. Am J Sports Med 42(11):2741–2750. doi:10.1177/0363546514547029

Farr J, Tabet SK, Margerrison E, Cole BJ (2014) Clinical, radiographic, and histological outcomes after cartilage repair with particulated juvenile articular cartilage: a 2-year prospective study. Am J Sports Med 42(6):1417–1425. doi:10.1177/0363546514528671

Fortier LA, Cole BJ, McIlwraith CW (2012) Science and animal models of marrow stimulation for cartilage repair. J Knee Surg 25(1):3–8

Gille J, Schuseil E, Wimmer J, Gellissen J, Schulz AP, Behrens P (2010) Mid-term results of autologous matrix-induced chondrogenesis for treatment of focal cartilage defects in the knee. Knee Surg Sports Traumatol Arthrosc 18(11):1456–1464. doi:10.1007/s00167-010-1042-3

Gille J, Behrens P, Volpi P, de Girolamo L, Reiss E, Zoch W, Anders S (2013) Outcome of autologous matrix induced chondrogenesis (AMIC) in cartilage knee surgery: data of the AMIC Registry. Arch Orthop Trauma Surg 133(1):87–93. doi:10.1007/s00402-012-1621-5

Gomoll AH, Madry H, Knutsen G, van Dijk N, Seil R, Brittberg M, Kon E (2010) The subchondral bone in articular cartilage repair: current problems in the surgical management. Knee Surg Sports Traumatol Arthrosc 18(4):434–447. doi:10.1007/s00167-010-1072-x

Gudas R, Gudaite A, Pocius A, Gudiene A, Cekanauskas E, Monastyreckiene E, Basevicius A (2012) Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. Am J Sports Med 40(11):2499–2508. doi:10.1177/0363546512458763

Hangody L, Dobos J, Balo E, Panics G, Hangody LR, Berkes I (2010) Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. Am J Sports Med 38(6):1125–1133. doi:10.1177/0363546509360405

Harris JD, Siston RA, Brophy RH, Lattermann C, Carey JL, Flanigan DC (2011) Failures, re-operations, and complications after autologous chondrocyte implantation--a systematic review. Osteoarthritis Cartilage 19(7):779–791

Henderson I, Lavigne P, Valenzuela H, Oakes B (2007) Autologous chondrocyte implantation: superior biologic properties of hyaline cartilage repairs. Clin Orthop Relat Res 455:253–261. doi:10.1097/01.blo.0000238829.42563.56

Kon E, Filardo G, Berruto M, Benazzo F, Zanon G, Della Villa S, Marcacci M (2011) Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. Am J Sports Med 39(12):2549–2557. doi:10.1177/0363546511420688

Kreuz PC, Erggelet C, Steinwachs MR, Krause SJ, Lahm A, Niemeyer P, Ghanem N, Uhl M, Sudkamp N (2006) Is microfracture of chondral defects in the knee associated with different results in patients aged 40 years or younger? Arthroscopy 22(11):1180–1186. doi:10.1016/j.arthro.2006.06.020

Kusano T, Jakob RP, Gautier E, Magnussen RA, Hoogewoud H, Jacobi M (2012) Treatment of isolated chondral and osteochondral defects in the knee by autologous matrix-induced chondrogenesis (AMIC). Knee Surg Sports Traumatol Arthrosc 20(10):2109–2115. doi:10.1007/s00167-011-1840-2

Lattermann C, Luckett MR (2011) Staging and comorbidities. J Knee Surg 24(4):217–224

Makris EA, Hadidi P, Athanasiou KA (2011) The knee meniscus: structure-function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 32(30):7411–7431. doi:10.1016/j.biomaterials.2011.06.037

Marcacci M, Filardo G, Kon E (2013) Treatment of cartilage lesions: what works and why? Injury 44(Suppl 1):S11–S15. doi:10.1016/S0020-1383(13)70004-4

McDermott ID, Amis AA (2006) The consequences of meniscectomy. J Bone Joint Surg 88(12):1549–1556. doi:10.1302/0301-620X.88B12.18140

Mithoefer K, Hambly K, Della Villa S, Silvers H, Mandelbaum BR (2009a) Return to sports participation after articular cartilage repair in the knee: scientific evidence. Am J Sports Med 37(Suppl 1):167S–176S. doi:10.1177/0363546509351650

Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR (2009b) Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med 37(10):2053–2063. doi:10.1177/0363546508328414

Nehrer S, Spector M, Minas T (1999) Histologic analysis of tissue after failed cartilage repair procedures. Clin Orthop Relat Res 365:149–162

Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH (2010) Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. Am J Sports Med 38(6):1110–1116. doi:10.1177/0363546509359067

Niemeyer P, Koestler W, Sudkamp NP (2011) Problems and complications of surgical techniques for treatment of full-thickness cartilage defects. Z Orthop Unfall 149(1):45–51. doi:10.1055/s-0030-1250104

Niemeyer P, Albrecht D, Andereya S, Angele P, Ateschrang A, Aurich M, Baumann M, Bosch U, Erggelet C, Fickert S, Gebhard H, Gelse K, Gunther D, Hoburg A, Kasten P, Kolombe T, Madry H, Marlovits S, Meenen NM, Muller PE, Noth U, Petersen JP, Pietschmann M, Richter W, Rolauffs B, Rhunau K, Schewe B, Steinert A, Steinwachs MR, Welsch GH, Zinser W, Fritz J (2016) Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: a guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU). Knee 23(3):426–435. doi:10.1016/j.knee.2016.02.001

Stanish WD, McCormack R, Forriol F, Mohtadi N, Pelet S, Desnoyers J, Restrepo A, Shive MS (2013) Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. J Bone Joint Surg Am 95(18):1640–1650. doi:10.2106/JBJS.L.01345

Steadman JR, Rodkey WG, Rodrigo JJ (2001) Microfracture: surgical technique and rehabilitation to treat chondral defects. Clin Orthop Relat Res (391 Suppl):S362–S369

Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP, TIG/ACT/01/2000&EXT Study Group (2011) Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 39(12):2566–2574. doi:10.1177/0363546511422220

Vavken P, Samartzis D (2010) Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: a systematic review of controlled trials. Osteoarthritis Cartilage 18(6):857–863. doi:10.1016/j.joca.2010.03.005

Widuchowski W, Widuchowski J, Trzaska T (2007) Articular cartilage defects: study of 25,124 knee arthroscopies. Knee 14(3):177–182. doi:10.1016/j.knee.2007.02.001

Zellner J, Angele P, Zeman F, Kujat R, Nerlich M (2013) Is the transplant quality at the time of surgery adequate for matrix-guided autologous cartilage transplantation? A pilot study. Clin Orthop Relat Res 471(9):2852–2861. doi:10.1007/s11999-013-2958-y

Zellner J, Krutsch W, Pfeifer CG, Koch M, Nerlich M, Angele P (2015) Autologous chondrocyte implantation for cartilage repair: current perspectives. Orthop Res Rev 7:149–158