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Operative Techniques in
Orthopaedics

Autologous Matrix-Induced Chondrogenesis and Generational Development of Autologous Chondrocyte Implantation

Hajo Thermann, MD, PhD,[*] Christoph Becher, MD,[†] Francesca Vannini, MD, PhD,[‡] and Sandro Giannini, MD[‡]

The treatment of osteochondral defects of the talus is still controversial. Matrix-guided treatment options for covering of the defect with a scaffold have gained increasing popularity. Cellular-based autologous chondrocyte implantation (ACI) has undergone a generational development overcoming the surgical drawbacks related to the use of the periosteal flap over time. As ACI is associated with high costs and limited in availability, autologous matrix-induced chondrogenesis, a single-step procedure combining microfracturing of the subchondral bone to release bone marrow mesenchymal stem cells in combination with the coverage of an acellular matrix, has gained increasing popularity. The purposes of this report are to present the arthroscopic approach of the matrix-guided autologous matrix-induced chondrogenesis technique and generational development of ACI in the treatment of chondral and osteochondral defects of the talus.

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Introduction

Chondral and osteochondral lesions are defects of the cartilaginous surface and underlying subchondral bone of the talar dome. These defects are often caused by a single or multiple traumatic events, mostly inversion or eversion ankle sprains in young, active patients.[1,2]

Owing to poor hyaline cartilage repair capability, chondral and osteochondral defects of the talus may lead to chronic symptoms with a reported frequency ranging from 17%-50%.[3-6] In fact, deep ankle pain associated with weight-bearing, limited range of motion, stiffness, catching, locking, and swelling of the affected joint are widely documented as a consequence of these defects.[7] These symptoms place the ability to walk, work, and perform sports at risk, and early osteoarthritis may develop.[3-8]

*Center for Hip, Knee and Foot Surgery, ATOS Clinic, Heidelberg, Germany.
†Department for Orthopaedic Surgery, Hannover Medical School, Hannover, Germany.
‡Rizzoli Orthopaedic Institute, Clinic I, University of Bologna, Bologna, Italy.
Address reprint requests to Hajo Thermann, MD, PhD, Center for Hip, Knee and Foot Surgery, ATOS Clinic, Heidelberg, Germany. E-mail: hajo.thermann@me.com

Cartilage repair may be obtained by cartilage replacement: (OATS, mosaicplasty) or with techniques aimed to generate a newly formed cartilage such as microfracture or autologous chondrocyte implantation (ACI).[9-17]

Arthroscopic debridement and bone marrow stimulation using the microfracture technique has proven to be an established, simple, and cost-effective operative treatment method for treating chondral and osteochondral defects of the talus with low morbidity.[10,11,18,19] Clinical trials and animal studies suggest the effectiveness of microfracture with filling of the defects with repair tissue, improvement of symptoms, and return to sports activities in athletes.[6,18,20,21] It is recommended as a first-line treatment, especially in defects measuring less than 1.5 cm^2.[11,19]

Autologous matrix-induced chondrogenesis (AMIC) by covering the microfractured area with a collagen membrane has gained increasing popularity. The defect is covered by a commercially available membrane with the goal of stabilizing the blood clot induced by the microfracture of the subchondral bone.[22,23]

Since its first publication in 1994, ACI has been established as a successful treatment method for articular cartilage defects. The procedure has been in clinical use since 1987 and was

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based on the implantation of a suspension of cultured autologous chondrocytes beneath a tightly sealed periosteal flap.[24] Despite the promising clinical results, some drawbacks especially related to the use of the periosteal flap have been reported.[25] Accordingly, the classical ACI technique has been modified in recent years and led to the formation of new generations of cell-based cartilage repair procedures. The use of 3-dimensional matrix scaffolds facilitated the procedure and has shown favorable biological properties.[13]

The purposes of this report are to present the arthroscopic approach of the matrix-guided AMIC technique and generational development of ACI in the treatment of chondral and osteochondral defects of the talus.

Autologous Matrix-Induced Chondrogenesis

This procedure can either be done open or arthroscopically. The advantage of an open procedure is the precise placement of the matrix and the easier possibility to address subchondral cysts with a bone graft. The advantages of the arthroscopic approach include fewer traumas to the soft tissues and omitting a malleolar osteotomy. In the following, the arthroscopic technique according to Thermann is described.[26] As a principle of this technique, the matrix is overlapping the defect after insertion and fixation with fibrin glue. Over time, the overlapping areas are debrided by movement of the ankle in flexion-extension resulting in a perfect sealing of the microfractured defect area (Fig. 1).

The procedure is performed under general anesthesia and a tourniquet placed at the thigh. Noninvasive distraction of the ankle is performed using bandages. Standard anteromedial and anterolateral portals are used. A 2.5- or 2.7-mm arthroscope is recommended. After limited synovectomy, the defect is prepared. All unstable cartilage is debrided, and sharp, perpendicular margins are created. The approximate size of the defect is determined using a calibrated probe by multiplying the longest longitudinal and transverse diameters in 1 measurement. The AMIC procedure is generally used in defects larger than 1 cm^2. With the arthroscopic awls of different angles, the microfractures are placed approximately 3-4-mm apart and 2-4-mm deep until fat droplets are evident. The portal for inserting the acellular collagen I-III matrix (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Schweiz) is enlarged to approximately 1 cm. The fluid is removed from the joint with small suction devices, and the defect is dried with small swabs. In larger cystic defects, autologous bone marrow aspirate from the iliac crest harvested with a Jamshidi needle can be inserted. The membrane is inserted by using a mosquito clamp (Fig. 2). The defect should be fully covered with the matrix overlapping all borders to achieve a sealing effect (Fig. 3). In deeper defects, the matrix can be doubled to better fill the defect area. Fibrin glue is inserted and the ankle kept in neutral position for 10 minutes. The wounds are closed in common fashion and a cast applied for 3-4 days to ensure stabilization of the clot and matrix in the defect and to prevent delamination. Afterwards, a common rehab program is started with partial weight-bearing for 6 weeks, increasing to complete weight-bearing at 8 weeks and continuous passive motion for 5-8 hours per day for 6 weeks.[10] At 4 months after surgery, the patients are allowed to resume low-impact sport activities. At 10 months after surgery, running and progressive training for high-impact activities such as tennis and soccer can be resumed.

Generational Development of ACI

As in AMIC, ACI can be performed arthroscopically or in an open procedure. In case of open surgery, malleolar osteotomy was necessary in the beginning and a periosteal flap was required to be sutured to the surrounding cartilage; this had considerable morbidity for the patients.[27] With the development of dedicated scaffolds, ACI in the ankle joint experienced a dramatic evolution, and arthroscopic implantation of a cell-seeded matrix was possible and is described in the following.

A first step for cartilage harvesting is required in all the patients treated by ACI. A small sample of cartilage (15-25 mg of cartilage tissue) is harvested arthroscopically directly from the affected ankle in a first-step arthroscopy, which also allows a direct evaluation and accurate measurement of the defect. The osteochondral detached fragment was proven to be a viable source of cells for ACI.[28] The cartilage is sent to the laboratory for cell expansion and is available for implantation 4 weeks later. A biodegradable scaffold based entirely on the benzylic ester of hyaluronic acid is used for cell support and proliferation (HYAFF 11, Fidia Advanced Biopolymers, Italy). This nonwoven 3-dimensional structure consists of a network of fibers of 10-15 μm in thickness with interstices of variable sizes, which constitute an optimal physical support to allow cell-to-cell contact, cluster formation, and extracellular matrix deposition.[29,30]

To permit an entirely arthroscopic procedure in the ankle, where the tangential perspective makes it uneasy when compared with the knee, a custom-made specific instrumentation was designed (CITIEFFE, Calderara di Reno, Italy). This

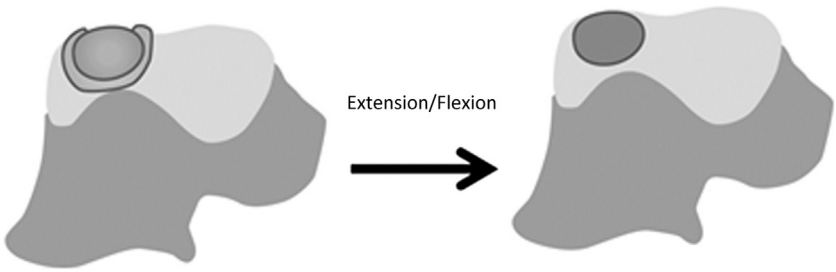

Figure 1 Principle of the arthroscopic AMIC technique. Perfect sealing of the defective area is achieved.

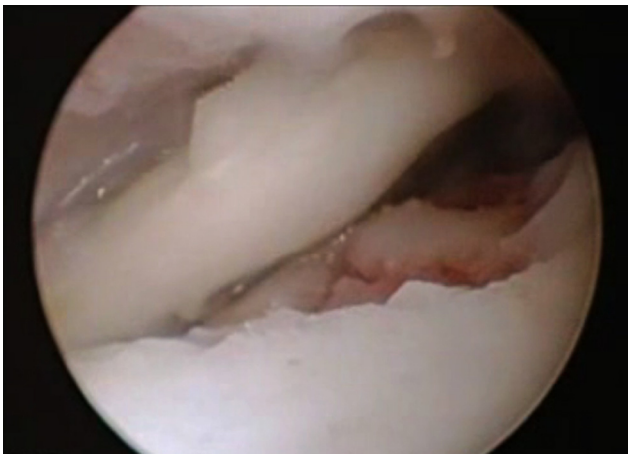

Figure 2 Insertion of the acellular matrix in the prepared defective area.

consisted of a stainless steel cannula that was 8 mm in diameter and 111 mm in length with a window on 1 side and a positioner specifically designed to slide inside the cannula delivering the scaffold directly to the site of lesion.[13]

Arthroscopic anterolateral and anteromedial approaches were used. The lesion site was trimmed to safeguard the integrity of the subchondral bone, and a sharp rim of healthy cartilage was defined and measured using a ruled probe. The autologous chondrocytes, seeded on a hyaluronic acid autoadhesive membrane (Fig. 4), are arthroscopically positioned on the lesions through the cannula (Figs. 5 and 6). The postoperative treatment is comparable with the AMIC technique.

Results

Autologous Matrix-Induced Chondrogenesis

In a prospective study, 48 patients were included.[26] The patients were examined at 6 months ($n = 43$), 1 year ($n = 32$), and 2 years ($n = 14$). Rating of the patients was performed with the Hannover Scoring System (HSS) for the ankle[31] and a Visual Analog Score (not scaled 10 cm, 0 = very poor, and 10 = excellent). The HSS incorporates clinical evaluation, functional performance, and subjective patient assessment. Assessment of cartilage was performed by magnetic resonance imaging (MRI).

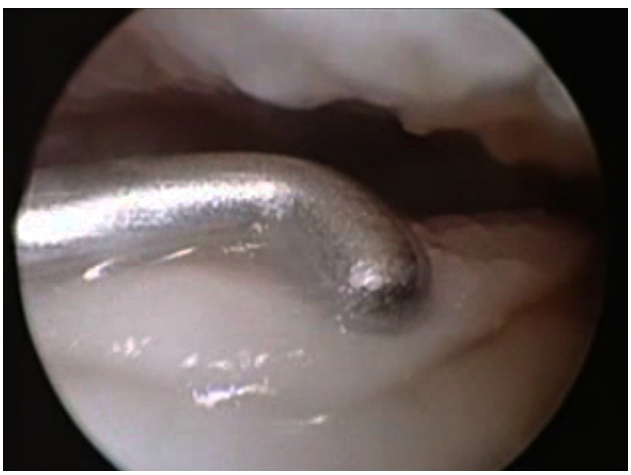

Figure 3 Shaping the matrix to the defect with overlapping the borders of the defective area.

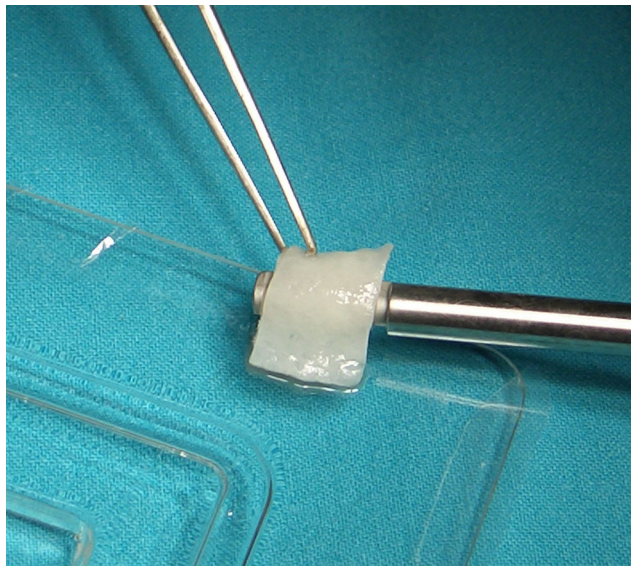

Figure 4 The HYAFF membrane with the chondrocytes is prepared to be delivered on the defect.

Among the 22 male and 26 female patients, the average age at the time of surgery was 37 years (range: 15-69 years). No complications were observed. One patient underwent revision at 9 months postoperatively with an arthroscopic artholysis owing to restricted range of motion with anterior soft tissue impingement. According to the HSS for the ankle, results improved from 53 ± 12 points preoperatively to 67 ± 16 at 6 months, 82 ± 16 at 1 year, and 89 ± 7 points at the 2-year follow-up examination (increase over time, $P \leq 0.008$). The mean Visual Analog Score for pain improved from 6.0 ± 2.7 preoperatively to 3.3 ± 2.8 at 6 months, 2.2 ± 2.7 at 1 year, and to 0.6 ± 1 at 2 years (decrease over time,

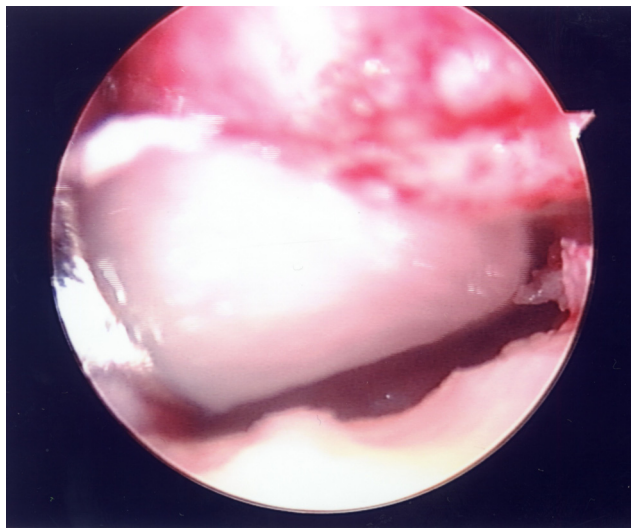

Figure 5 The membrane is sliding through the cannula in the ankle joint.

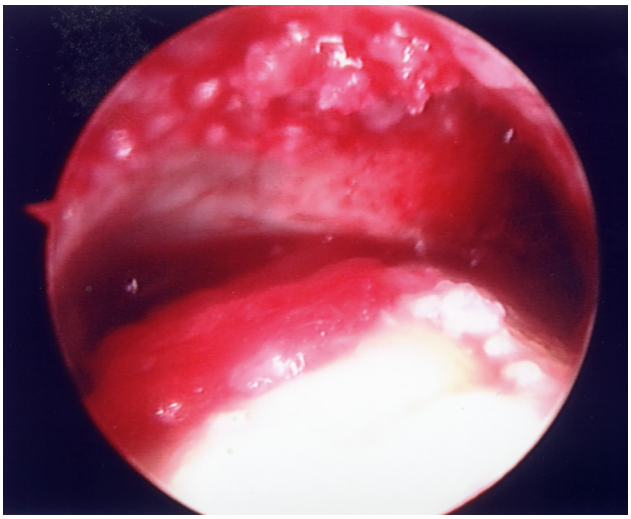

Figure 6 The membrane is finally positioned on the defect. (Color version of figure is available online.)

$P \leq 0.001$). Function improved from 3.7 ± 2.4 preoperatively to 7.1 ± 2.8 at 6 months, 7.6 ± 3.0 at 1 year, and 9.1 ± 0.9 at 2 years (increase over time, $P \leq 0.002$). Satisfaction improved from 2.6 ± 2.6 preoperatively to 7.3 ± 3.1 at 6 months, 7.6 ± 3.2 at 1 year, and to 9.4 ± 0.5 at 2 years (increase over time, $P \leq 0.003$). On MRI, no delamination of the matrices was observed with filling of the defects with repair tissue and good integration to adjacent cartilage (Figs. 7 and 8).

Autologous Chondrocyte Implantation

In a retrospective case series of 46 patients, all patients were clinically evaluated using the American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Scoring System (AOFAS) preoperatively and at 12, 36 months, and final follow-up of

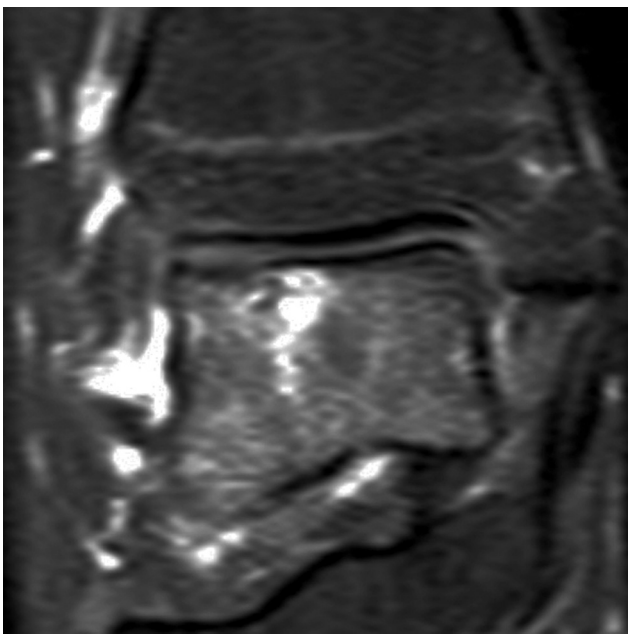

Figure 7 Coronal magnetic resonance image displaying an osteochondral defect preoperatively.

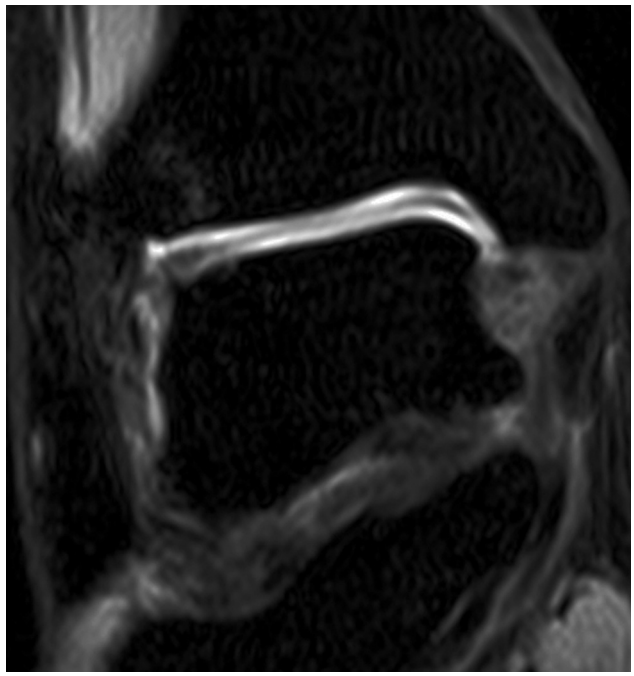

Figure 8 Coronal magnetic resonance image obtained 2 years after AMIC showing recovery of the subchondral bone and excellent defect fill.

87.2 ± 14.5 months.[32] The results were rated as follows: excellent (90-100), good (80-89), fair (60-79), and poor (inferior to 60).[33] Plain radiographs and MRI scans were also taken preoperatively and at the scheduled follow-up. Assessment of cartilage was performed by the Magnetic Resonance Observation of Cartilage Repair Tissue scoring system.[34] No intraoperative or postoperative complications were reported.

The mean preoperative AOFAS score was 57.2 ± 14.3. At the 12-month follow-up, the mean AOFAS score was 86.8 ± 13.4 ($P = 0.0005$); at 36 months after surgery, the mean score was 89.5 ± 13.4 ($P = 0.0005$); and at final follow-up of 87.2 ± 14.5 months, it was 92.0 ± 11.2 ($P = 0.0005$). The overall scores at final follow-up were rated as 29 excellent, 9 good, 3 fair, and 1 poor. All the 3 cases rated as fair have been previously operated for cartilage repair procedures (mosaicplasty in 1 case and microfracture in the other 2 cases). The case rated as poor at follow-up was a 41-year-old patient with no associated lesions or previous interventions. One patient was lost at final follow-up. We experienced 3 failures at 41, 43, and 51 months of follow-up. All these patients had been previously treated by cartilage repair techniques, before receiving ACI (microfracture in 2 cases and chondrectomy in 1 case).

Radiographic results at follow-up demonstrated no increase in arthritis in all the cases. MRI performed at final follow-up according to the Magnetic Resonance Observation of Cartilage Repair Tissue scoring system showed nearly complete integration of the regenerated tissue with the surrounding cartilage in most cases. Qualitative MRI T2 mapping was used in 20 cases of this series. Based on the T2 values described in the healthy control group, a repair tissue with a mean T2 map value of 35-45 ms was considered compatible with the normal hyaline

cartilage and was found in all the cases treated, covering a mean percentage of 69% ± 22% of the repaired lesion area. Tissue with T2 map value of 35 ms, expression of a fibrocartilaginous regenerative tissue, was found in limited foci in most patients (17.2% ± 16.6% of the repaired site). In 3 patients (15%), there was no evidence of fibrocartilage, and only in 1 patient (5%), fibrocartilage was found in 62% of the repaired lesion area.[35]

Discussion

The history of cartilage regeneration in osteochondral lesions of the talar dome spans approximately 10 years. Over this time, a series of evolution steps rendered techniques less invasive, less expensive, and simpler in overcoming all the major drawbacks. Arthroscopic ACI and AMIC are safe procedures with low complication rates. The results obtained with the described procedures were excellent or good in more than 80% of cases and did not show any negative tendency over time.

ACI was first used in the treatment of osteochondral lesions of the knee, becoming increasingly popular, and it was later successfully applied to the ankle.[13,27,36-39] Open-field ACI in the ankle was technically demanding as an open surgery with malleolar osteotomy and a periosteal flap sutured to the surrounding cartilage were required, with considerable morbidity.[27] Nevertheless, impressive results were obtained even in large lesions. Furthermore, these patients have the longest follow-up of the series, and the stability of their result over time is noticeable.[37]

A biodegradable 3-dimensional scaffold for cell support and proliferation, developed following recent tissue engineering improvements, permitted a shift to a completely arthroscopic procedure. Arthroscopic implantation, firstly implemented in the knee, was modified to be used in the ankle, owing to the development of an instrumentation able to overcome the disadvantages given by the tangential perspective and the narrow space available.[13] However, when comparing the clinical results of matrix-associated autologous chondrocyte transplantation (ACT) and classical ACT using a periosteal flap, clinical evaluation after matrix-associated ACT at the knee appear does not result in significantly superior result than those obtained by the classical ACT technique.[40,41] However, negative effects such as periosteal hypertrophy were not observed with matrix-associated ACT.

The need of 2 surgical operations and the high costs are considered major drawbacks of ACI, which lead in search of new methods of repair. The AMIC technique implies certain advantages over ACI. It is a single surgery and cartilage culturing after initial chondrocyte harvesting and a second-stage reimplantation is not needed. The matrix used with the described arthroscopic technique is a readily available "off-the-shelf" item. However, whether the results are superior to arthroscopic microfracture alone has not been proven yet. Good clinical and radiological results were reported in an open approach in conjunction with autologous bone grafting after a follow-up of 24 months.[22] Whether filling of the defect with bone is necessary remains uncertain.

Recently, bone marrow–derived cells (BMDCs), have been indicated as a new option for the treatment of articular osteochondral defects.[42] The idea to transplant the entire bone marrow cellular pool permits the cells to be processed directly in the operating room, without the need for a laboratory phase, and allowing BMDCs transplantation to be performed in "1 step" instead of the 2 steps required for ACI. The results of the treatment of osteochondral defects of the talus in 48 patients at a mean follow-up of 24 months were promising, suggesting that the 1-step technique is an alternative for cartilage repair,[42] and they were lately confirmed by a T2 mapping qualitative study.[35]

The evidence level for all techniques evaluated in cartilage repair of the talus is still low. No prospective randomized or comparative matched paired studies have been published yet. Thus, no conclusions can be made if 1 technique is superior to the other. All techniques described appear to improve function and symptoms in the treatment of chondral or osteochondral defects of the talus. Several studies indicate that a defect size greater than 1.5 cm^2 results in inferior defect fill and inferior clinical findings after microfracture alone.[43-45] Thus, the use of a sealing matrix appears to be beneficial for stabilizing the clot and results might be even superior if the matrix was seeded with autologous chondrocytes or BMDCs.

Conclusions

The techniques proposed are minimally invasive with little soft tissue trauma, they omit malleolar osteotomy and appear to result in a durable repair with a satisfactory clinical outcome over time. Advancements achieved with the use of matrices and the advent of tissue engineering and stem cell technologies are promising. However, as superiority of the use of matrices and cell-based techniques have not been proven yet in the use for chondral and osteochondral defects of the talus, prospective randomized trials or at least comparative matched paired studies must be performed in the future to justify the ongoing use in the treatment of talar defects.

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