# 11 New and Emerging Techniques in Cartilage Repair: Matrix-Induced Autologous Chondrocyte Implantation (MACI)

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Autologous chondrocyte implantation (ACI) was originally developed based on the work of Smith, who cultured chondrocytes ex vivo [1]. Grande et al. treated full-thickness cartilage defects with expanded chondrocytes and showed viable chondrocytes and hyaline-like repair tissue on histology [2]. Initially successful in treating osteochondral defects (OCD) in the knee [3], ACI has subsequently been adopted for treatment of osteochondral lesions of the talus (OLT).

ACI is a two-stage procedure in which healthy chondrocytes are harvested arthroscopically from nonessential areas such as the loose osteochondral fragment, the periphery of the OLT, or the ipsilateral knee intercondylar notch. The authors prefer to use the ipsilateral intercondylar notch due to decreased cartilage-forming capacity of the excised osteochondral fragment [4] and concern for creating a new OLT by biopsy of the talus [5]. The harvested chondrocytes are sent to a commercial laboratory to be cultured and expanded into millions of cells. In the second stage, the isolated and expanded chondrocytes are implanted into the prepared OLT under a harvested periosteal patch that is sealed with 6-0 sutures and fibrin glue.

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More recently, modifications have been made to the original technique to try to reduce its associated pitfalls. Matrix-induced autologous chondrocyte implantation (MACI) obviates the need for periosteal patch harvest by using a biodegradable scaffold to retain chondrocytes and theoretically reduce leakage [6]. Periosteal donor site morbidity and postoperative patch hypertrophy can thus be avoided. The cultured chondrocytes are dispersed on a porcine collagen type I/III scaffold which is then implanted onto the osteochondral lesion. This procedure will be further discussed in detail later in this chapter.

Currently, MACI is approved by the Food and Drug Administration for use in the knee. Contraindications include a history of hypersensitivity to aminoglycosides or porcine material, malalignment that would increase stress on the graft, advanced osteoarthritis, history of inflammatory arthritis, and uncorrected blood coagulation disorders.

There are still no large comparative blinded studies of MACI for OLTs, and the evidence for its use is currently limited to level IV case series.

## 11.1 Patient Selection

Patients with OLTs who have failed extensive nonsurgical management including physical therapy, bracing, casting, and nonsteroidal anti-inflammatory medication should be considered



G. L. Canata et al. (eds.), *Sports Injuries of the Foot and Ankle*,
https://doi.org/10.1007/978-3-662-58704-1_11

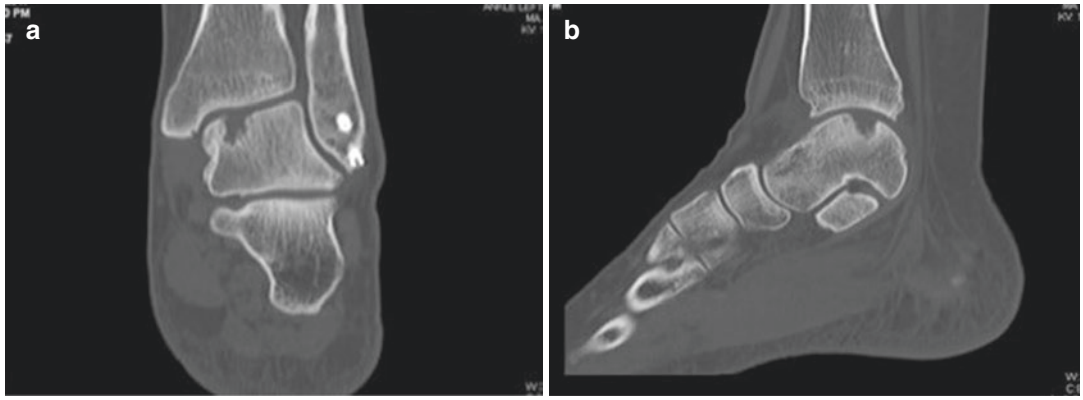


**Fig. 11.1** Preoperative CT of a left ankle with a cystic osteochondral lesion. (**a**) Coronal view demonstrating medial location of the cystic osteochondral lesions. (**b**) Sagittal view showing the cystic osteochondral lesion in approximately the middle of the medial talus

for a cartilage transplant. MACI should be considered for an OLT between 1.07 and 4 $cm^2$. MACI is also indicated for patients who have failed marrow stimulation procedures. Additionally, if the lesion is deeper than 6 mm, bone graft augmenting of the lesion should be considered [7]. Worse outcomes have been reported when the lesion is more than 7 mm in depth, and this should be kept in mind when indicating patients with these lesions for MACI [8]. Unipolar lesions involving only the talus are preferred.

## 11.2 Imaging

Preoperative imaging should include standard weight-bearing anteroposterior, mortise, and lateral plain films. Stress radiographs with Telos device should be performed if ligamentous injury is suspected.

Magnetic resonance imaging (MRI) should be routinely performed. It is useful to evaluate the articular cartilage, subchondral bone, and periarticular soft tissues.

Computed tomography (CT) with 3D reconstructions is helpful for localizing and accurately measuring the size of the lesion, especially if there are associated cysts. CT images represent the true size of the lesion, absent the obscuring bone edema often seen on MRI (Fig. 11.1a, b).

## 11.3 Equipment

For the first phase, supine ankle arthroscopy is performed through anteromedial, anterolateral, and posterolateral portals using 30 and 70° 2.7 mm arthroscopes with noninvasive soft tissue distraction [9]. A 1.9 mm 30° arthroscope may be used for tight joints. For the cartilage harvest in the knee, ring curettes and arthroscopic graspers are used, as well as a cannula for graft harvest.

## 11.4 Positioning

In the first phase, the ankle arthroscopy is performed in the supine position. All padding should be removed from the leg of the table and the nonoperative leg should be padded independently, allowing for clearance between the operative ankle and the table. The knee and hip are both flexed at around 45° and held in place with a Ferkel Thigh Holder (Smith & Nephew). The ankle is distracted with a sterile soft tissue distractor (Guhl Non-Invasive Ankle Distractor, Smith & Nephew).

In the second phase, when the open procedure is done, the ankle is positioned based on the surgical approach to the lesion.

## 11.5 Surgical Procedure

The first phase of the procedure includes a diagnostic ankle arthroscopy using previously described techniques to evaluate the lesion and confirm that MACI treatment is appropriate. Debridement of non-involved parts of the ankle can then be performed, but the lesion should be left alone until the second stage. At the same time, the cartilage biopsy is removed from the ipsilateral knee intercondylar notch. From standard knee arthroscopy portals, cartilage is harvested from the lateral aspect of the intercondylar notch by a sharp ring curette (a 200–300 mg sample is necessary). Care is taken to avoid detaching the cartilage completely so that it does not float free in the knee joint. A tissue grasper is then used to remove the cartilage piece with a gentle twisting motion and removed out a cannula to prevent its entrapment in the anterior soft tissue. The tissue is then stored in packaging provided by and as instructed by the Vericel Corporation (Vericel, Cambridge, Massachusetts).

The second phase of the procedure is the implantation phase. This is typically performed at a minimum of 6–12 weeks after the cells have been cultured and placed onto the membrane. In most cases, the implant is available for 5 years after biopsy. Implantation can be performed by open surgery or occasionally by arthroscopically. The size and location of the lesion will often dictate which approach is optimal. Arthroscopic results have so far been promising, with multiple studies showing good short- and medium-term results [6, 10, 11].

### 11.5.1 Traditional Open Surgery

A tourniquet is placed to ensure the surgical field remains bloodless. The location of the lesion determines the positioning of the patient. Medial lesions are positioned supine and a bump is placed under the contralateral hip. A medial malleolar osteotomy is performed to gain access to the lesion. First, the medial malleolus is predrilled for two 4.0 mm cancellous lag screws or a medial malleolar hook plate (Fig. 11.2). Then, under fluoroscopy, a guide pin is used as a cutting guide for the saw to assist in making the osteotomy in exactly the correct plane (Fig. 11.3). Imaging should confirm that the saw will exit lateral to the extent of the OLT so that the entire lesion can be accessed.

If the lesion is lateral, it can be accessed by predrilling the fibula for two interfragmentary lag screws and then making an oblique fibular

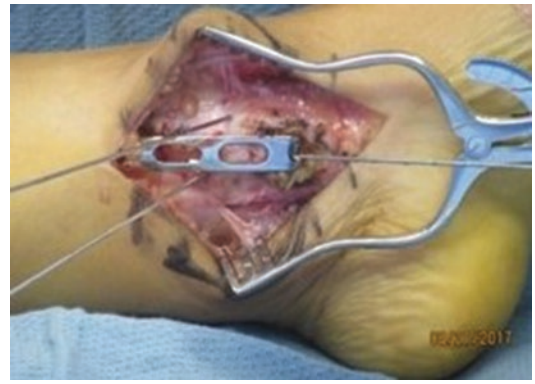

**Fig. 11.2** Predrilling the medial malleolus for a medial malleolar osteotomy, utilizing a hook plate for reduction after insertion of the MACI graft

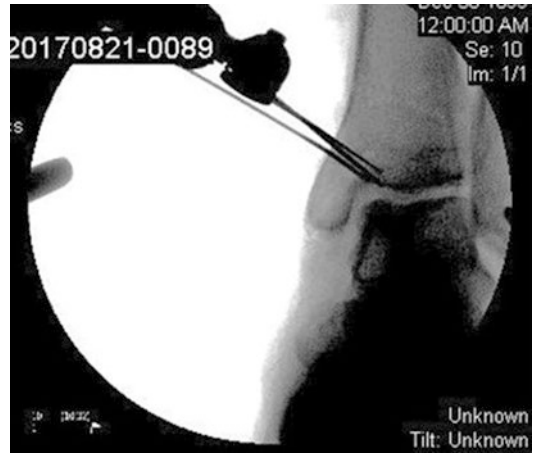


**Fig. 11.3** Fluoroscopic X-ray demonstrating inserting guide pins in the correct planes. The saw tip is then placed on the guide pins to assist with the appropriate location of the medial malleolar osteotomy

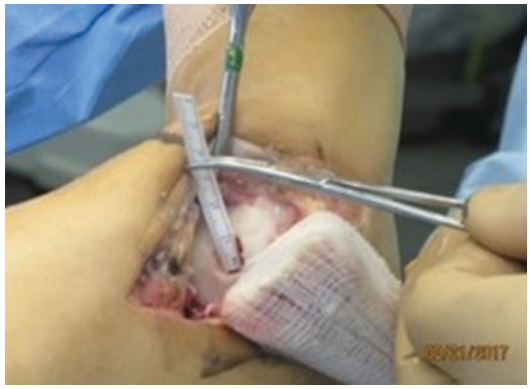

**Fig. 11.4** After excising the osteochondral lesion, the defect is measured with a ruler to get the exact dimensions for preparation of the MACI graft

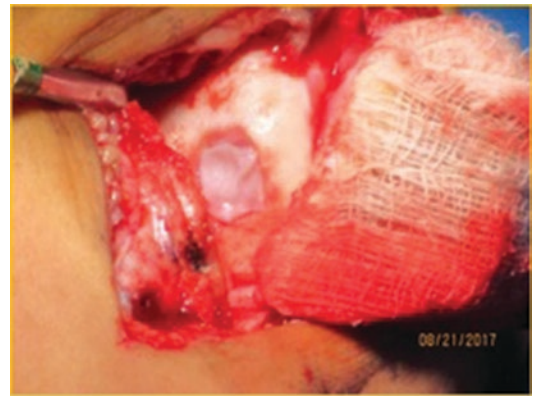


**Fig. 11.5** The MACI graft is self-adherent but sometimes a few stitches are used to further secure it to the osteochondral lesion bed. Pictured is the graft in the medial talar dome of a left ankle prior to fibrin glue insertion

osteotomy. Releasing the anterior talofibular ligament and the anterior capsule allows for the fibula to be rotated posteriorly. A cuff of tissue is left on the fibula for latter Brostrom-type repair of the lateral ligaments.

After adequate exposure is obtained, the OLT can then be debrided to stable vertical margins. A 15 blade can be used to obtain sharp vertical borders. The subchondral bone must be left intact in order to prevent osseous bleeding. After deflating the tourniquet, the lesion is dried with thrombin-soaked pledgets. The lesion is then measured to determine the exact size of the defect (Fig. 11.4). A sterile suture foil package is then pressed into the defect to form a template. The MACI membrane is then cut to match this template. After further drying with thrombin, the membrane is then placed onto the lesion and pressed gently into place, ensuring that the cell side is facing down into the lesion (Fig. 11.5). Fibrin glue is then applied to the membrane, sealing it in place. After the fibrin has been set (5–7 min), range of motion testing should then be performed to ensure that the MACI graft is stable. 6-0 Vicryl sutures can be applied for additional security, but are rarely needed because the membrane is self-adherent.

The osteotomy is then reduced and repaired. An additional transverse screw at the proximal portion of the medial malleolar osteotomy is used for additional fixation due to the oblique nature of the osteotomy. If a hook plate is utilized, it is secured with compression across the medial malleolar osteotomy (Fig. 11.6a, b). Lateral osteotomies can be fixed with a neutralization one-third tubular plate after placing the interfragmentary lag screws. The incisions are then closed with 3-0 Vicryl sutures, followed by 4-0 nylon vertical mattress sutures. The leg is then placed in a well-padded short-leg cast that is subsequently split with the cast saw in the recovery room.

## 11.6 Arthroscopic Technique

Due to the less technically demanding nature of the MACI procedure, it is reasonable to perform entirely arthroscopically, thereby avoiding the morbidity of an osteotomy. The all arthroscopic second stage procedure is performed with the same setup and through the same portals as the first stage. After debridement of any loose cartilage fragments and synovitis, debridement of the lesion should occur at this time, using arthroscopic different-angled curettes to obtain stable vertical borders. The lesion is then accurately measured and the MACI graft cut to size. Next, the arthroscopic fluid flow is stopped and all fluid is drained from the ankle joint. Thrombin-soaked pledgets are inserted from the portal closest to the lesion and used to dry the lesion.

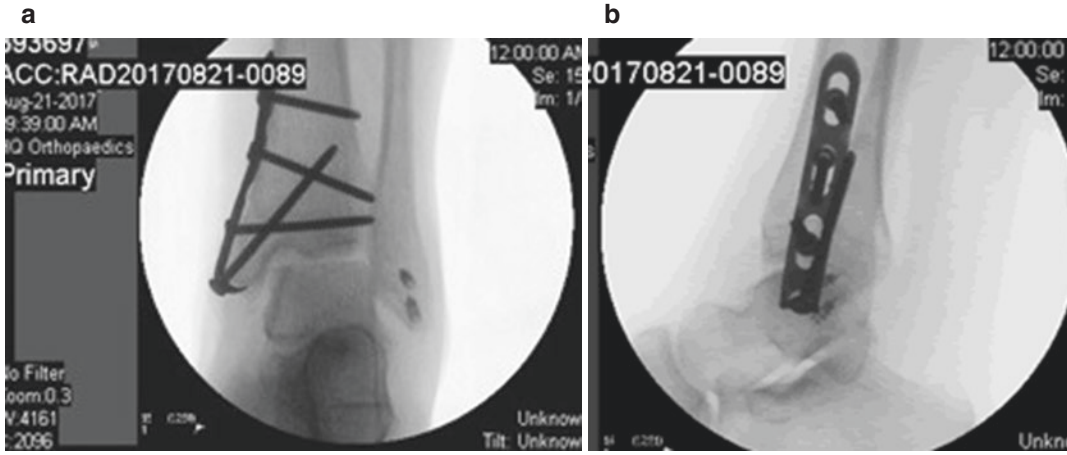


**Fig. 11.6** Reduction of the medial malleolar osteotomy. (**a**) AP X-ray demonstrating the appropriate location of the hook plate and screws to reduce and compress the medial malleolar osteotomy. (**b**) Lateral radiograph demonstrates the plate located in the medial of the distal tibia and medial malleolus

Arthroscopic forceps or a specialized cannula delivery system can be used to deliver the matrix into the ankle joint [12]. A probe and a freer elevator can then be used to place the matrix onto the lesion and precisely fit it into the lesion. Fibrin glue should then be placed over the matrix with a commercially available applicator. Once the fibrin is set (5–7 min), the ankle is then taken through extension and flexion to ensure that matrix is stable. All instruments should then be removed and the portals closed with 4-0 nylon vertical mattress sutures.

## 11.7 Postoperative Protocol

The importance of a comprehensive protocol for postoperative care and rehabilitation cannot be overstated. The physician, patient, and physical therapist must work as a team and be in close contact during the process. The goals are to promote effective healing of the surgical site and cartilage graft and to then return the patient to a high level of function. There is a paucity of good evidence in the literature, so much of the information is based off of animal models as well as accepted information of cartilage physiology [13]. It is also reasonable to extrapolate information from ACI/MACI in the knee. Most authors agree that supervision by a skilled physical therapist is necessary and on the general concepts to follow [14].

The rehabilitation process can be divided into four phases [15]:

1. Phase 1 is the "healing phase," surgery to week 6.
2. Phase 2 is the "transitional phase," weeks 6–12.
3. Phase 3 is the "remodeling phase," weeks 12–32.
4. Phase 4 is the "maturation phase," weeks 32–52.

The following protocol is for first-generation ACI, but for newer techniques, quicker advancement can be considered because they don't rely on periosteal patch graft containment.

Phase 1: Surgery to Week 6

Cast and sutures are removed at 2 weeks postsurgery. A compression stocking is applied, and the patient is placed in a controlled ankle motion (CAM) walking boot. They are allowed to start partial weight bearing up to 30 lb. Range of motion exercises are initiated at week 2 and focus on the sagittal plane. At 4 weeks stationary bike with no resistance is begun. Weight bearing is increased toward full weight bearing in a CAM boot at week 6, and osteotomy healing must be checked. They are transitioned to a lace-up

figure-of-eight brace and supportive athletic shoes when the osteotomy is healed. Formal physical therapy is then initiated. Phase 1 is designed to recover full range of motion while protecting the healing graft. Motion and light compressive forces are needed for healthy chondrocytes [16].

Phase 2: Weeks 6–12

The musculature around the ankle is strengthened under close direction of the physical therapist. Resistance can be added to the stationary bicycle, and proprioceptive exercises are begun. Isometric followed by eccentric strengthening exercises are included in this phase. The basis for this increase in resistance is that the implanted chondrocytes are maturing and can undergo increased compressive loading. An increase in strength and proprioception are needed in order to progress to more demanding activities.

Phase 3: Weeks 12–32

Patients can now increase their activity level and strengthening. Both walking speed and duration can be increased, as long as their pain and swelling allows. No jogging or running is allowed. Strengthening exercises in weight-bearing positions are started. This phase serves to increase strength and endurance while maintaining range of motion, which are needed for sports-specific training. The graft is still maturing in this phase, and 30 min of weight-bearing exercise without pain and swelling is necessary in order to graduate to phase 4.

Phase 4: Weeks 32–52

Cross-training and return-to-sport activities are begun. By 8 months, the graft should tolerate high-impact activities. The therapist can supervise an increase in intensity and duration, with symptoms such as pain and swelling guiding progression. Due to extended periods of immobilization and slow progression in the prior phases, the patient may be generally deconditioned, and generous rest periods between sessions should be standard. Unrestricted activity can begin 12 months after surgery, bearing in mind that the graft continues to mature and remodel for up to 2 years from the time of surgery [17].

## 11.8 Results

Previously, we have reported on our results of ACI of the talus [11, 18]. Outside the United States, Schneider and Karaikudi did MACI on 20 patients, with a mean follow-up of 21 months. The mean size of the lesions was 233 $mm^2$. The AOFAS scores improved from 60 to 87, but there were two failures and six patients with no improvement in pain [6]. Magnan et al. treated 30 patients with MACI, with a mean OLT size of 236 $m^2$. The AOFAS score improved from 37 to 84, with a follow-up of 45 months. However, only 50% of the patients returned to their previous sporting activity [19]. More recently, Kreulen et al. reported on 7-year follow-up of nine patients who had failed previous arthroscopic treatment for an osteochondral lesion of the talus. The average OLT size was 129 $mm^2$. The AOFAS score went from 62 to 78, and the SF-36 score showed significant improvements in physical functioning, lack of bodily pain, and social functioning, compared with preoperative data [20]. Brittberg et al. studied MACI versus microfracture of the knee in a prospective randomized trial and published results in 2014 and 2018 in the same group. At an average follow-up of 5 years, the symptomatic knee cartilage defects 3 $cm^2$ or greater treated with MACI were significantly improved over microfracture [21, 22].

## 11.9 Complications

Infection, bleeding, wound breakdown, neurovascular injury, and continued symptoms are possible in any foot and ankle surgery. Graft and patch hypertrophy are specific complications of ACI, but are decreased in second- and third-generation ACI techniques such as MACI [23]. If an osteotomy is performed, nonunion and hardware-related pain are possible complications.

Pearls:

1. If performing an osteotomy, ensure that direct perpendicular access to the entirety of the lesion is maintained. The osteotomy site should exit the plafond lateral to a medial OLT and medial to a lateral OLT.

2. A thorough debridement of all diseased tissue from the lesion is necessary, and stable vertical walls should be obtained.
3. Concomitant ankle malalignment or instability must be corrected.
4. Be prepared to perform an open procedure with or without an osteotomy in the event that the lesion proves to not be amenable to arthroscopic MACI graft placement.

## References


1. Smith A. Survival of frozen chondrocytes isolated from cartilage of adult mammals. Nature. 1965;205:782–4.
2. Grande DA, Pitman MI, Peterson L, Menche D, Klein M. The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation. J Orthop Res. 1989;7(2):208–18.
3. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. Am J Sports Med. 2010;38(6):1117–24.
4. Candrian C, Miot S, Wolf F, et al. Are ankle chondrocytes from damaged fragments a suitable cell source for cartilage repair? Osteoarthr Cartil. 2010;18(8):1067–76.
5. Wodicka R, Ferkel E, Ferkel R. Osteochondral lesions of the ankle. Foot Ankle Int. 2016;37(9):1023–34.
6. Schneider TE, Karaikudi S. Matrix-induced autologous chondrocyte implantation (MACI) grafting for osteochondral lesions of the talus. Foot Ankle Int. 2009;30(9):810–4.
7. Petersen L, Brittberg M, Lindahl A. Autologous chondrocyte transplantation of the ankle. Foot Ankle Clin. 2003;8:291–303.
8. Choi WJ, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? Am J Sports Med. 2009;37(10):1974–80.
9. Ferkel RD. Foot and ankle arthroscopy. 2nd ed. Philadelphia: Wolters Kluwer; 2017.
10. Giza E, Sullivan M, Ocel D, et al. Matrix-induced autologous chondrocyte implantation of talus articular defects. Foot Ankle Int. 2010;31(9):747–53.
11. Nam EK, Ferkel RD, Applegate GR. Autologous chondrocyte implantation of the ankle: a 2 to 5 year follow-up. Am J Sports Med. 2009;37:274–84.
12. Giannini S, Buda R, Ruffilli A, et al. Arthroscopic autologous chondrocyte implantation in the ankle joint. Knee Surg Sports Traumatol Arthrosc. 2014;22:1311–9.
13. Hambly K, Bobic V, Wondrasch B, Van Assche D, Marlovits S. Autologous chondrocyte implantation postoperative care and rehabilitation: science and practice. Am J Sports Med. 2006;34(6):1020–38.
14. Larsen NJ, Sullivan M, Ferkel RD. Autologous chondrocyte implantation for treatment of osteochondral lesions of the talus. Oper Tech Orthop. 2014;24(3):195–209.
15. Antkowiak T, Ferkel R, Sullivan M, Kreulen C, Giza E, Whitlow S. Rehabilitation after cartilage reconstruction. In: van Dijk CN, Kennedy JG, editors. Talar osteochondral defects. Berlin, Germany: Springer; 2014. p. 135–44.
16. Brittberg M, Peterson L, Sjogren-Jansson E, Tallheden T, Lindahl A. Articular cartilage engineering with autologous chondrocyte transplantation. A review of recent developments. J Bone Joint Surg Am. 2003;85-A(Suppl 3):109–15.
17. Giannini S, Buda R, Vannini F, Di Caprio F, Grigolo B. Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: surgical technique and results. Am J Sports Med. 2008;36(5):873–80.
18. Kwak SK, Kern BS, Ferkel RD, et al. Autologous chondrocyte implantation of the ankle: 2 to 10-year results. Am J Sports Med. 2014;42:2156–64.
19. Magnan B, Somalia E, Bondi M, et al. Three-dimensional matrix-induced autologous chondrocyte implantation for osteochondral lesions of the talus: midterm results. Adv Orthop. 2012;2012:942174.
20. Kreulen C, Giza E, Walton J, Sullivan M. Seven year follow-up of matrix-induced autologous transplantation in talus articular defects. Foot Ankle Spec. 2018;11:133–7.
21. Brittberg M, Recker D, Ilgenfritz J, Saris DBF. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. Am J Sports Med. 2018;46:1343–51.
22. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. Am J Sports Med. 2014;42:1384–94.
23. Gomoll AH, Probst C, Farr J, Cole BJ, Minas T. Use of a type I/III bilayer collagen membrane decreases reoperation rates for symptomatic hypertrophy after autologous chondrocyte implantation. Am J Sports Med. 2009;37(Suppl 1):20S–3S.