Advances in Cartilage Repair

Mohammad T. Azam, BS[a], James J. Butler, MB BCh[a], Matthew L. Duenes, MD[a], Thomas W. McAllister, MBBS[a,b], Raymond C. Walls[a], Arianna L. Gianakos, DO[a], John G. Kennedy, MD, MCh, MMSc, FFSEM, FRCS (Orth)[a,*]

KEYWORDS

• Ankle osteochondral lesion • Microfracture • Autologous osteochondral transplantation • Biologics

KEY POINTS

- Osteochondral lesions of the ankle joint are difficult to manage because of the poor regenerative ability of the articular cartilage and, thus, are typically managed surgically.
- Lesions that are small (<100 mm^2 or <10 mm) can be treated with less invasive procedures such as arthroscopic debridement, anterograde drilling, scaffold-based therapies, and augmentation with biological adjuvants.
- Caution should be taken when utilizing bone marrow stimulation via microfracture as it produces an unstable fibrocartilage infill and damages the underlying subchondral plate.
- For patients with large lesions (>100 mm^2 or >10 mm), cystic lesions, uncontained lesions, or patients in whom prior bone marrow stimulation has failed, management with autologous osteochondral transplantation is indicated.
- Biological adjuvants such as platelet-rich plasma, concentrated bone marrow aspirate, and hyaluronic acid can accelerate the regenerative process, but definitive guidelines regarding their role are yet to be determined.

Video content accompanies this article at http://www.orthopedic.theclinics.com.

INTRODUCTION

Osteochondral lesions (OCLs) of the ankle joint are characterized by injury to the articular cartilage and/or underlying subchondral bone.[1] This debilitating pathology is often preceded by acute trauma such as ankle sprains or fractures, or can be precipitated by chronic, repetitive microtrauma to the joint.[1] Nontraumatic etiologies include spontaneous necrosis, generalized ligamentous laxity, systemic vasculopathies, metabolic disorders, and embolic disease.[2] Patients present with deep ankle pain, swelling, altered gait, and concomitant ankle instability.[1] Diagnosis is often delayed because of a low index of suspicion together with poor sensitivity of plain film radiographs for detecting OCLs.[3] Although computed tomography (CT) scans allow for excellent visualization of the subchondral bone, they are limited in their evaluation of the articular cartilage.[4] MRI is the gold standard imaging modality and has a sensitivity and specificity of 96% for detecting OCLs at the ankle.[4] It permits detailed assessment of the articular cartilage (Table 1), the subchondral bone, and any concomitant soft tissue pathology. However, MRI may overestimate the size of the lesion because of subchondral bone

[a] Foot and Ankle Division, Department of Orthopaedic Surgery, NYU Langone Health, 171 Delancey Street, New York, NY 10002, USA; [b] University of Cambrdige School of Clinical Medicine, Box 111 Cambridge Biomedical Campus, Cambridge CB2 0SP, UK
* Corresponding author.
E-mail address: john.kennedy@nyulangone.org

Orthop Clin N Am 54 (2023) 227–236
https://doi.org/10.1016/j.ocl.2022.11.007

Table 1
MRI classification for osteochondral lesions of the talus

Stage	Definition
1	Articular cartilage damage only
2a	Cartilage injury with underlying fracture and surrounding bony edema
2b	Stage 2a without surrounding bony edema
3	Detached but nondisplaced fragment
4	Detached and displaced fragment
5	Subchondral cyst formation

marrow edema that extends beyond the margin of the lesion.[4]

Outcomes following conservative management of ankle OCLs are unsatisfactory because of the poor regenerative biology of the avascular articular cartilage and limited blood supply to the talus and subchondral bone.[5,6] Conventionally, surgical management of ankle OCLs is determined by lesion size.[6] Surgical options described for smaller lesions (<10 mm in diameter or <100 mm^2) include arthroscopic debridement, bone marrow stimulation (BMS), scaffold-based therapies and augmentation with biological adjuvants such as platelet-rich plasma (PRP), concentrated bone marrow aspirate (CBMA), or hyaluronic acid (HA).[6,7] Replacement procedures, such as autologous osteochondral transplantation (AOT), are indicated for patients with large lesions (>10 mm in diameter or >100 mm^2), cystic lesions, uncontained lesions, or for patients who have failed a prior reparative procedure such as BMS.[8]

This article describes the most recent clinical evidence regarding the various treatment modalities for ankle OCLs. It also details the limitations associated with each therapeutic option.

REPARATIVE

BMS via microfracture is a widely used surgical intervention for OCLs of the ankle and knee joint.[9] Various surgical instruments such as a pick, awl, or drill are used to perforate the subchondral plate stimulating the aggregation of mesenchymal stem cells (MSCs) at the defect site, and, in response to growth factors, BMS promotes the generation of fibrocartilaginous tissue.[10,11] BMS has been used in lesions of varying sizes; however, the International Congress on Cartilage Repair of the Ankle consensus meeting in 2018 demonstrated that BMS may not be suitable in patients with an OCL greater than 100 mm^2 or greater than 10 mm in diameter.[12] Although favorable results have been demonstrated following BMS for smaller lesions at short- to midterm follow-up,[13] there remains concern regarding degradation of the repair tissue over time.

The hyaline cartilage at the ankle joint is predominantly composed of type-II collagen and high levels of proteoglycans.[14] The fibrocartilage tissue produced by BMS is histologically comparable to native hyaline cartilage during the initial 6 weeks following BMS.[15] Eventually, numerous biological alterations occur, including de-differentiation of type-II collagen into type-I collagen, reduced expression of proteoglycans, and tissue fibrillation, ultimately producing a hyaline-like substance.[15] This hyaline-like material is less resilient, less durable and, ultimately, inferior in comparison to the native hyaline cartilage and is susceptible to degradation from shear forces.[10] Although improvement in subjective outcomes have been reported, numerous studies found degradation of the reparative fibrous cartilage over time. Lee and colleagues[16] performed second-look arthroscopies 1 year following BMS and found that 30% of their cohort demonstrated adequate integration of the repair tissue with the adjacent native tissue. Furthermore, MRI obtained 5 years following BMS demonstrated fibrillation of the fibrocartilage tissue in all patients.[17]

The subchondral plate and subchondral bone play a crucial role in the preservation of the ankle joint. The subchondral bone functions as a structural scaffold bearing 30% of the compressive load through the joint, compared to the 1% to 3% of load absorbed by the articular cartilage.[5] In addition, the subchondral bone communicates with the articular cartilage via cross-talk to facilitate a variety of signaling pathways.[18] Concerns have been raised regarding the integrity of the subchondral plate following BMS. Chen and colleagues[19] conducted a rabbit study and found that microfracture induced bone fracturing and compaction with profound osteocyte necrosis in the adjacent bone. Orth and colleagues[20] performed BMS in sheep and reported a reduction in bone volume and trabecular thickness, with an increase in subchondral cysts and intralesional osteophytes. In addition, a systematic review by Seow and colleagues[21] found that BMS produced significant histological changes and reduced density of the architecture of the deep subchondral bone. These findings have been replicated in clinical

studies. Kennedy and colleagues followed a cohort of 42 patients who underwent BMS for OCLs of the talus (OLTs). Despite an initial improvement in foot and ankle outcome score (FAOS), there was a reduction in FAOS at final follow-up of 51.7 months.[5] Furthermore, there was a significant decrease in the subchondral bone health score as assessed via MRI at final follow-up with increased subchondral cyst formation.[5]

Unfortunately, the methodological quality of many of the studies is poor, with marked heterogeneity and under-reporting of data between the studies. Therefore, caution must be taken when evaluating these outcomes.

REGENERATIVE

Regenerative techniques for ankle OCLs include autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), and autologous matrix-induced chondrogenesis (AMIC). These procedures are often utilized after failed microfracture or for larger lesions not amenable to BMS.

ACI is a 2-stage procedure that was first used to manage chondral defects in the knee.[22] The first stage of ACI involves harvesting hyaline cartilage from a non-weight bearing portion of the knee or the anterior talus. The harvested chondrocytes are then isolated, and the extracellular matrix is enzymatically removed. The cells are then cultured and expanded in vitro for 11 to 21 days, where the cells dedifferentiate and return to a fetal stage. During the second stage, the cells are directly implanted into the OCL, and a periosteal patch is sewn over the defect to contain the suspended cells and provide growth factors to promote chondrogenesis. Brittberg and colleagues[22] performed ACI in patients with full-thickness knee OCLs. The authors reported good subjective outcomes at final follow-up with approximately 80% of knees expressing type-II collagen with the appearance of hyaline cartilage. Overall clinical success at 10-year follow-up has been reported 89.9%; however, the procedure has multiple drawbacks.[23,24] ACI requires 2 procedures and a wide exposure to perform the periosteal sleeve, which includes osteotomy and graft site morbidity. Additionally, in a study by Kwak and colleagues, [23] 86% of patients required removal of hardware, and 38% had periosteal softening and hypertrophy.

MACI is a regenerative technique that embeds cultured autogenous chondrocytes in a matrix of either type-I/III collagen, hyaluronan, or polyglycolic acid, which is secured with fibrin glue.[25] Implantation can be performed arthroscopically, avoiding periosteal harvest morbidity and reliance on suture fixation. There are more viable cells delivered to the lesion compared with ACI, which is susceptible to leakage and uneven distribution. Patients undergoing MACI have comparable clinical scores to ACI.[26] Most patients have mean improvements in AOFAS scores ranging from 13 to 24 up to 12-year follow-up.[25,26] Similar to ACI, MRI findings do not necessarily correlate with the clinical outcomes. Although clinical results of MACI procedures are overall positive, limitations remain, most notably the need for 2 procedures and cost.

AMIC is a single-stage cartilage repair technique with promising results.[27] The procedure involves microfracture with application of an exogenous scaffold, such as a collagen type-I/III bilayer. By utilizing a matrix, the chondrogenic clot induced by BMS is covered, stabilized, and provides an early 3-dimensional scaffold to seed MSCs. Additionally, biological augments can be included in the scaffold via CBMA or PRP to further promote hyaline cartilage formation. In a case series performed by Weigelt and colleagues,[28] 33 patients underwent an open AMIC procedure with a mean follow-up of 4.7 years, mean AOFAS score of 93, and a 79% return to sport rate. The matrix can be loaded into lesions arthroscopically, with reported AOFAS scores of 20 point improvements at 2 years.[29] When directly comparing ACI, MACI, and AMIC for OLTs, all 3 groups have similar clinical outcome scores at short-term follow-up.[30] Additionally, second-look arthroscopy has demonstrated continuous, intact cartilaginous layers filling the defects with type-II collagen identified in biopsies. AMIC appears to be an attractive alternative to ACI and MACI, because it is a single procedure, more cost-effective, and circumvents morbidity associated with grafts and harvesting chondrocytes. However, longer term follow-up is still limited.

Extracellular matrix allografts (ECMA) can also be utilized to augment BMS. BioCartilage (Arthrex Inc., Nas, Florida) is a dehydrated, micronized allogenic cartilage ECMA that contains type-II collagen and proteoglycans.[31] It provides a scaffold for MSCs to infiltrate and produce a higher quality cartilage infill. Fortier and colleagues[32] reported in an equine model microfracture augmented with PRP, and BioCartilage produced an infill with significantly better ICRA histology score and MRI T2 relaxation times than microfracture alone. Furthermore, Kennedy and colleagues[33] utilized

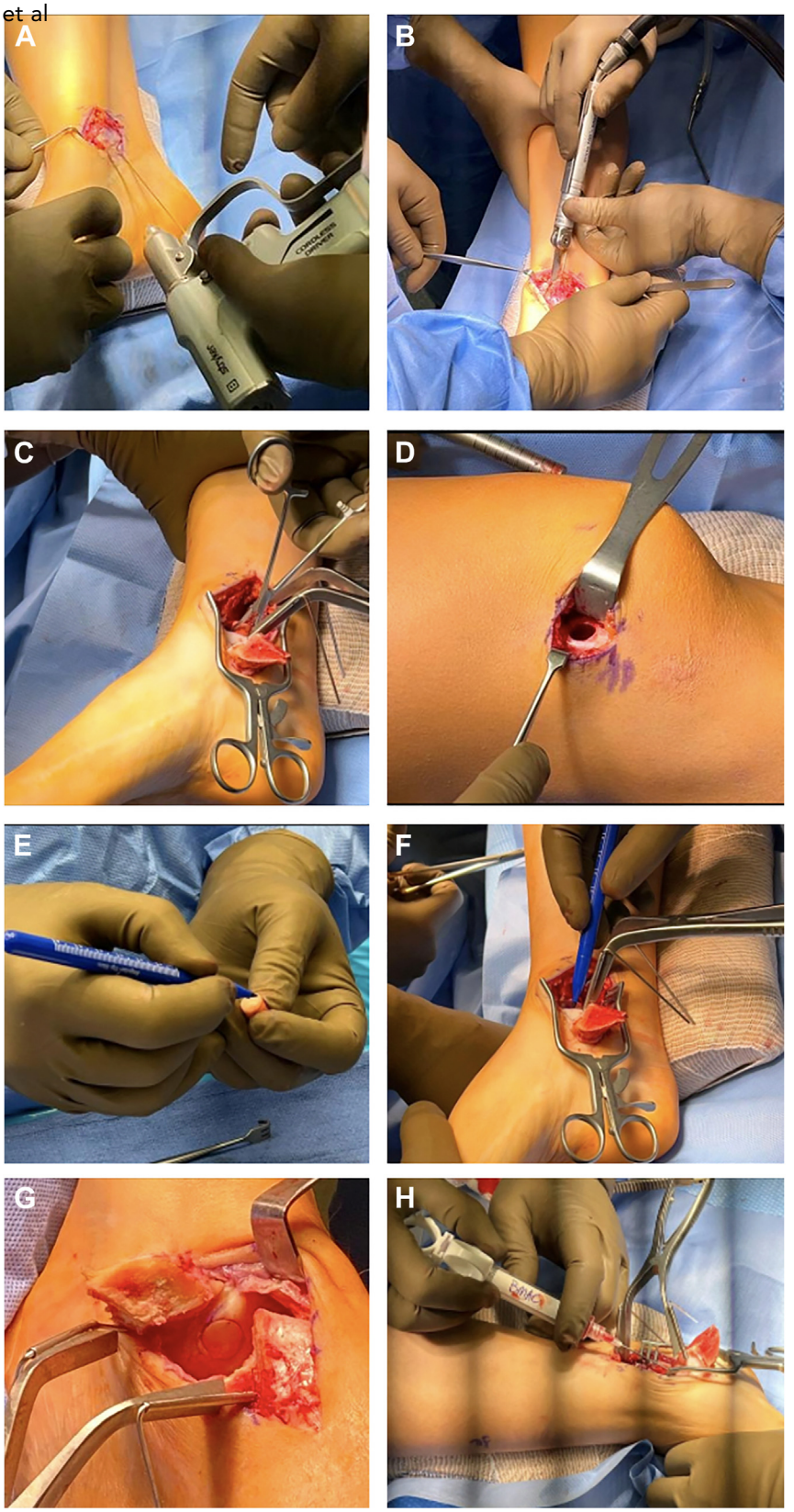

Fig. 1. (*A*) Prior to making the osteotomy cut, a provisional K wire is drilled into the medial malleolus at angle of 30° relative to the long axis of the tibia. Next, the medial malleolus is predrilled with 2 parallel fixation holes (*B*) An oscillating saw is used to create a Chevron-type osteotomy, which is continued for 7/8s of the bone. The saw is stopped at the level of the subchondral bone. The osteotome is then completed using a sharp half-inch osteotome.

BioCartilage and CBMA to augment BMS. At 20 months follow-up on MRI, they found 87.6% of patients who had BioCartilage had comte infill of their defect compared with 46.5% for BMS without BioCartilage. Longer-term studies will be needed to determine whether ECMA provides robust cartilage repair that will be sustained over a longer period than BMS alone.

REPLACEMENT

Replacement strategies including AOT are indicated in patients with larger lesions (area >100 mm^2 or diameter >10 mm), cystic lesions, uncontained lesions, or patients who have failed previous BMS.[8] AOT offers many advantages to reparative and regenerative techniques by removing and replacing not only the damaged overlying cartilage, but also the critical subchondral plate and bone, providing a more comprehensive solution.[2] Autograft transplant is the senior surgeon's preferred method in comparison to allograft transfer. In their comparative study, Kennedy and colleagues reported poorer clinical outcomes and poor host graft integration on MRI in the allograft group.[34] Similarly, a meta-analysis by Migliorini and colleagues[35] found autograft to have lower failure and rates compared with allograft at midterm follow-up.

AOT involves resection of the diseased cartilage and underlying subchondral bone in a cylinder shape from the talus and is subsequently replaced with an autograft harvested from the non-weight bearing portion of the lateral femoral condyle. OLTs that are medially located can be accessed through a chevron-type medial malleolar osteotomy. For lateral lesions, a tibial trapezoidal osteotomy can be utilized to gain access to all but the most posterior lesions, avoiding a fibular takedown (Fig. 1).[36]

Several studies have reported favorable outcomes following AOT (Fig. 2). In a cohort of 72 patients, Murawski and colleagues[36] reported a significant improved in FAOS scores at 28 months follow-up and an average RTS of 12 weeks. Furthermore, T2 mapping on MRI 1 year after AOT demonstrated restoration of the radius of curvature and color stratification similar to that of native cartilage. Similarly, for larger OLTs in the athletic population, Nguyen and colleagues[37] reported significant improvement in visual analog scale (VAS) scores at 45 months follow-up, with 87% of patients returning to previous level of sport.

BIOLOGICAL ADJUVANTS

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous blood product generated by centrifugation of peripheral blood to produce an increased concentration of platelets. PRP consists of growth factors including fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor, platelet-derived growth factor, and transforming growth factor-β (TGF-β1).[38] These growth factors and cytokines play key roles in MSC chemotaxis, target cell activation, cell proliferation, neoangiogenesis, and cartilage matrix production, and provide an additional immuno-modulatory benefit.[38]

Several studies have examined the potential chondroprotective effects of PRP when used in conjunction with either BMS or AOT. The combination of BMS and PRP has been shown to promote a supportive biological environment encouraging chondrocyte synthesis and an increase in type-II collagen deposition.[39] A randomized controlled trial (RCT) by Gormeli and colleagues[40] showed a statistically significant increase in AOFAS scores and decreased VAS scores for patients with OLTs treated with BMS and PRP compared to BMS and HA injections and a saline control group. Furthermore, an RCT by Guney and colleagues[41] found significantly improved clinical outcomes in the cohort treated with BMS and PRP compared with BMS alone. However, a systematic review by Seow and colleagues[42] found there were a limited

(*C*) Following release and reflection of the bone and soft tissue, a modified retractor is used to facilitate adequate exposure of the medial aspect of the talar surface. For lateral lesions, a tibial trapezoidal osteotomy can be utilized to gain access to all but the most posterior lesions, avoiding a fibular takedown. (*D*) A mini-open arthrotomy is used to harvest the donor plug from the lateral non-weight bearing portion of the ipsilateral femoral condyle, which is then bathed in CBMA. For lesions greater than 10 mm in diameter, 2 grafts are used. The 2 grafts are placed side by side in a figure-of-8 or half-moon configuration, which allows the fibrocartilage to fill in the nonadjacent space of the graft. The base of the graft recipient is overdrilled by 2 mm using an acorn-shaped drill tip so as to maintain articular congruency during the postoperative maturation and remodeling process. (*E–G*) Both the donor plug and the highest point of the peripheral margin of the OCL are marked with a pen. The graft should be gently placed into the most congruent position possible. (*H*) The ankle is then injected with CBMA.

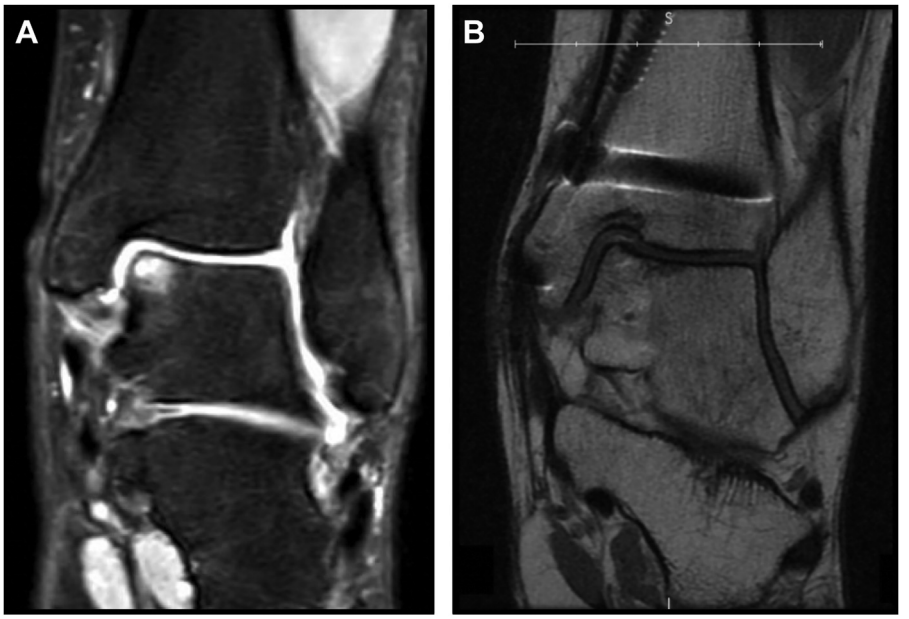

Fig. 2. (*A*) 21-year-old female runner presented with a 1-year history of left ankle pain following an acute ankle inversion injury. Her MRI (*A*) demonstrated a 12 mm × 6 mm cystic osteochondral lesion at the shoulder of the medial talus. She subsequently underwent autologous osteochondral transplantation with injection of CBMA. She had a repeat MRI (*B*) of the left ankle at 4 months postoperatively, which demonstrated satisfactory integration of the donor graft into the recipient talar dome.

number of comparative studies evaluating the role of PRP in BMS, warranting future research. There appears to be limited data regarding the role of PRP as an adjunct to AOT procedures. Boakye and colleagues[43] found elevated levels of TGF-β1 in rabbits that underwent AOT procedure with concomitant PRP compared with those that did not receive PRP. Additionally, Smyth and colleagues[44] showed improved graft integration and higher mean ICRS scores in those who underwent AOT with adjuvant PRP compared with AOT alone.

In summary, PRP is a readily available resource that promotes cartilage repair and type-II collagen deposition supported by basic scientific princis and clinical research. However, there is significant variability between patients, preparation techniques, and overall poor quality of evidence, which makes analysis of the overall literature challenging.[45]

Concentrated Bone Marrow Aspirate

Traditional theory suggested that MSCs differentiated directly into osteoblasts and chondrocytes to support cartilage repair.[46] However, new evidence proposes that most MSCs are engulfed by macrophages and form a secretome–a paracrine signaling apparatus–which promotes regenerative processes via immunomodulatory effects such as down regulation of proinflammatory interleukin (IL)-1β gene expression.[47] CBMA contains a potent anti-inflammatory, IL-1 receptor antagonist protein, which prevents activation of inflammatory cytokine cascades.[47] CBMA contains many growth factors such as TGFβ, which promotes chondrogenic differentiation of MSCs and type-II collagen formation.[48]

CBMA is a useful adjunct to BMS, as the addition of MSCs and growth factors into a cartilage defect promotes a hyaline-like repair and increased type-II collagen deposition. This has been demonstrated in animal models, particularly in equine medicine.[49,50] Fortier and colleagues[49] compared the results of microfracture alone to microfracture and CBMA in an equine model and found improved radiological and histological repair in the CBMA group. The use of CBMA in conjunction with BMS has produced encouraging outcomes.[14,51] Hannon and colleagues[14] compared outcomes for patients with OLTs treated with BMS and CMBA or BMS alone and found significantly improved FAOS and MOCART (magnetic resonance observation of cartilage repair tissue) scores in the CBMA group. Radiologically the

CBMA group showed increased infilling of the lesion, and over 95% had comte integration, with lower rates of fissuring than the BMS-only group. Murphy and colleagues[51] found a statistically significant decrease in the revision rate for the BMS and CBMA cohort.

Mercer and colleagues[52] found that in patients treated with AOT for OLTs, the addition of CBMA alone produced comparable results to CBMA plus ECMA, suggesting that CBMA alone provides sufficient augmentation for successful graft integration. Furthermore, Kennedy and colleagues[53] demonstrated that CBMA reduces postoperative subchondral cysts following AOT.

Hyaluronic Acid

HA is a high-molecular weight polysaccharide glycosaminoglycan. HA is found naturally in the synovial fluid and is responsible for maintaining the viscoelastic properties of joints, reducing friction, and transmitting shear forces.[7]

In addition to its beneficial rheological properties, HA plays an important biological role enhancing proliferation of chondrocytes and stimulating chondroitin sulfate synthesis, an important component of proteoglycans.[7] HA has been proposed as a useful adjunct to BMS for cartilage repair[54] and has exhibited chondroprotective and anti-inflammatory properties in animal studies.[55] This is supported by clinical outcome data, which report improved functional and MRI outcomes for patients undergoing BMS, although HA appears to be inferior to PRP in this regard.[40]

Recent advances include the use of HA-based cell-free bioscaffolds (HACS) such as Hyalofast (Anika Therapeutics Inc., Bedford, Massachusetts), which trap MSCs.[56] This supports a paracrine signaling environment that mediates angiogenesis, cell survival, and differentiation, improving the healing capacity of the cartilage and preventing fibrosis.[57] Histological studies show an increase in hyaline-like cartilage formation.[57] Clinical data report improvements in pain scores and radiological outcomes, especially when HACS is used in conjunction with BMS and CBMA.[58]

FUTURE DEVELOPMENTS

In-office nano-arthroscopy (IONA) is a novel needle arthroscopic system that facilitates inspection, evaluation, and treatment of a diseased joint using a 2.2 mm arthroscope and sheath.[59] These procedures are conducted with wide awake local anesthetic no tourniquet (WALANT), facilitating rapid recovery and return to daily activities. The IONA system utilizes an optic chip at the tip of the camera, which provides high-quality, high-resolution (400 $\times$ 400 pixel) images with a 120° field of view.[59] In addition, surgical tools such as graspers, shavers, burrs, probes, scissors, and resectors can be used with the IONA technology to manage the specific pathology. IONA procedures are carried out at the bedside with the patient fully conscious, providing feedback to the surgeon.

The exact role of IONA for the management of OCLs of the ankle joint has not yet been determined, primarily because of its recent resurgence. IONA can directly visualize the OCL and may offer a more precise assessment of the size of the lesion than that obtained on conventional MRI. In addition, IONA can be used to inspect the entire ankle joint to identify and treat any concomitant pathologies that may not have been captured on MRI. At their institution, the authors have utilized IONA to directly treat smaller OCLs with debridement, drilling, and delivery of biological adjuvants such as PRP, CBMA, and scaffold-based therapies such as ECMA (Video 1).

Ankle impingement secondary to excessive scar tissue formation is commonly encountered following routine ankle surgery, including surgical intervention for OCLs of the ankle joint.[59] Patients frequently present with ankle pain with restricted dorsiflexion at the ankle joint. A recent study by Colasanti and colleagues[59] described the utility of IONA in the debridement of this cicatrized tissue. This retrospective study of 31 patients reported significant improvement in PROMIS (Patient-Reported Outcomes Measurement Information System) scores and FAOS scores at final follow-up, with 96% returning to sport at a mean time of 3.9 weeks. In patients who present with ankle impingement following surgical intervention for ankle OCLs, IONA can be an effective tool to simultaneously resect the excessive scar tissue and to evaluate the integrity of the repaired articular cartilage and/or autograft (Video 2).

SUMMARY

An osteochondral lesion of the ankle joint is a challenging pathology to treat in light of the limited self-regenerative capacity of the articular cartilage. Smaller lesions ($<$100 mm^2 or $<$10 mm) can be managed with less invasive procedures such as arthroscopic debridement, anterograde drilling, and augmentation with biological adjuvants. Care should be taken

when considering treating the OCL with BMS because of the inferior fibrocartilage infill that is produced together with the damage to the underlying subchondral plate. Large lesions (>100 mm^2 or >10 mm), cystic lesions, uncontained lesions, or a failed prior BMS procedure warrant a replacement procedure such as an AOT. AOT has been shown to produce excellent results at long-term follow-up, with reported success rates of over 90%. Biological adjuvants such as PRP, CBMA, and HA are promising treatment modalities that can augment the cartilaginous regenerative process, but the precise indication for each biologic is yet to be determined.

CLINICS CARE POINTS

- The current gold standard diagnostic imaging modality is MRI, but it can overestimate the size of the OCL.
- Lesion size is a major factor in deciding the appropriate treatment strategy
- Smaller lesions (<100 mm^2 or <10 mm) can be managed with less invasive procedures such as arthroscopic debridement, anterograde drilling, and augmentation with biological adjuvants.
- BMS via microfracture damages the underlying subchondral plate and also produces an inferior fibrocartilage infill that degenerates over time.
- Indications for AOT include: large lesions (>100 mm^2 or >10 mm), cystic lesions, uncontained lesions, or patients who have failed prior BMS.
- Biological adjuvants such as PRP, CBMA, and HA have been demonstrated to accelerate the regenerative process, but definitive guidelines regarding their role have yet to be determined.

DISCLOSURE

The authors report the following potential conflicts of interest or sources of funding: J.G. Kennedy is a consultant to Arteriocyte Industries (Isto Biologics) and Arthrex Inc., and receives support from Ohnell Family Foundation and Mr. and Mrs. Michael J. Levitt. J.G. Kennedy reports as a board or committee member for the American Orthopaedic Foot and Ankle Society, European Society of Sports Traumatology, Knee Surgery and Arthroscopy, Ankle and Foot Associates, and International Society for Cartilage Repair of the Ankle.

SUPPLEMENTARY DATA

Supmentary data related to this article can be found online at https://doi.org/10.1016/j.ocl.2022.11.007.

REFERENCES

1. Barbier O, Amouyel T, de l'Escalopier N, et al. Osteochondral lesion of the talus: what are we talking about? Orthop Traumatol Surg Res 2021;107(8s):103068.
2. O'Loughlin PF, Heyworth BE, Kennedy JG. Current concepts in the diagnosis and treatment of osteochondral lesions of the ankle. Am J Sports Med 2010;38(2):392–404.
3. Hamilton C, Burgul R, Kourkounis G, et al. Osteochondral defects of the talus: radiological appearance and surgical candidate profiling - A retrospective analysis. Foot (Edinb) 2021;46:101767.
4. Looze CA, Capo J, Ryan MK, et al. Evaluation and management of osteochondral lesions of the talus. Cartilage 2017;8(1):19–30.
5. Shimozono Y, Coale M, Yasui Y, et al. Subchondral bone degradation after microfracture for osteochondral lesions of the talus: an MRI analysis. Am J Sports Med 2018;46(3):642–8.
6. Lan T, McCarthy HS, Hulme CH, et al. The management of talar osteochondral lesions - current concepts. J Arthrosc Jt Surg 2021;8(3):231–7.
7. Kawasaki K, Ochi M, Uchio Y, et al. Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels. J Cell Physiol 1999;179(2):142–8.
8. Ramponi L, Yasui Y, Murawski CD, et al. Lesion size is a predictor of clinical outcomes after bone marrow stimulation for osteochondral lesions of the talus: a systematic review. Am J Sports Med 2017;45(7):1698–705.
9. Park JH, Park KH, Cho JY, et al. Bone marrow stimulation for osteochondral lesions of the talus: are clinical outcomes maintained 10 years later? Am J Sports Med 2021;49(5):1220–6.
10. Murawski CD, Foo LF, Kennedy JG. A review of arthroscopic bone marrow stimulation techniques of the talus: the good, the bad, and the causes for concern. Cartilage 2010;1(2):137–44.
11. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. Clin Orthop Relat Res 2001;(391 Suppl):S362–9. https://doi.org/10.1097/00003086-200110001-00033.

12. Smyth NA, Murawski CD, Adams SB Jr, et al. Osteochondral allograft: proceedings of the international consensus meeting on cartilage repair of the ankle. Foot Ankle Int 2018;39(1_Suppl):35s–40s.
13. Rikken QGH, Dahmen J, Reilingh ML, et al. Outcomes of bone marrow stimulation for secondary osteochondral lesions of the talus equal outcomes for primary lesions. Cartilage 2021;13(1_Suppl): 1429s–37s.
14. Hannon CP, Ross KA, Murawski CD, et al. Arthroscopic bone marrow stimulation and concentrated bone marrow aspirate for osteochondral lesions of the talus: a case-control study of functional and magnetic resonance observation of cartilage repair tissue outcomes. Arthroscopy 2016;32(2):339–47.
15. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. J Bone Joint Surg Am 1993; 75(4):532–53.
16. Lee KB, Bai LB, Yoon TR, et al. Second-look arthroscopic findings and clinical outcomes after microfracture for osteochondral lesions of the talus. Am J Sports Med 2009;37(Suppl 1):63s–70s.
17. Becher C, Driessen A, Hess T, et al. Microfracture for chondral defects of the talus: maintenance of early results at midterm follow-up. Knee Surg Sports Traumatol Arthrosc 2010;18(5):656–63.
18. Madry H, van Dijk CN, Mueller-Gerbl M. The basic science of the subchondral bone. Knee Surg Sports Traumatol Arthrosc 2010;18(4):419–33.
19. Chen H, Sun J, Hoemann CD, et al. Drilling and microfracture lead to different bone structure and necrosis during bone-marrow stimulation for cartilage repair. J Orthopaedic Res 2009;27(11):1432–8.
20. Orth P, Goebel L, Wolfram U, et al. Effect of subchondral drilling on the microarchitecture of subchondral bone: analysis in a large animal model at 6 months. Am J Sports Med 2012;40(4):828–36.
21. Seow D, Yasui Y, Hutchinson ID, et al. The subchondral bone is affected by bone marrow stimulation: a systematic review of preclinical animal studies. Cartilage 2019;10(1):70–81.
22. Brittberg M, Lindahl A, Nilsson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 1994;331(14):889–95.
23. 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(9):2156–64.
24. Giannini S, Buda R, Ruffilli A, et al. Arthroscopic autologous chondrocyte implantation in the ankle joint. Knee Surg Sports Traumatol Arthrosc 2014; 22(6):1311–9.
25. Lenz CG, Tan S, Carey AL, et al. Matrix-induced autologous chondrocyte implantation (MACI) grafting for osteochondral lesions of the talus. Foot Ankle Int 2020;41(9):1099–105.
26. 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.
27. Lee YH, Suzer F, Thermann H. Autologous matrix-induced chondrogenesis in the knee: a review. Cartilage 2014;5(3):145–53.
28. Weigelt L, Hartmann R, Pfirrmann C, et al. Autologous matrix-induced chondrogenesis for osteochondral lesions of the talus: a clinical and radiological 2- to 8-year follow-up study. Am J Sports Med 2019;47(7):1679–86.
29. Giannini S, Buda R, Battaglia M, et al. One-step repair in talar osteochondral lesions: 4-year clinical results and t2-mapping capability in outcome prediction. Am J Sports Med 2013;41(3):511–8.
30. Giannini S, Buda R, Cavallo M, et al. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. Injury 2010;41(11):1196–203.
31. Riff AJ, Davey A, Cole BJ. Emerging technologies in cartilage restoration. In: Yanke AB, Cole BJ, editors. Joint preservation of the knee: a clinical casebook. Cham (Switzerland): Springer International Publishing; 2019. p. 295–319.
32. Fortier LA, Chapman HS, Pownder SL, et al. BioCartilage improves cartilage repair compared with microfracture alone in an equine model of full-thickness cartilage loss. Am J Sports Med 2016; 44(9):2366–74.
33. Shimozono Y, Williamson ERC, Mercer NP, et al. Use of extracellular matrix cartilage allograft may improve infill of the defects in bone marrow stimulation for osteochondral lesions of the talus. Arthroscopy 2021;37(7):2262–9.
34. Shimozono Y, Hurley ET, Nguyen JT, et al. Allograft compared with autograft in osteochondral transplantation for the treatment of osteochondral lesions of the talus. J Bone Joint Surg Am 2018; 100(21):1838–44.
35. Migliorini F, Maffulli N, Baroncini A, et al. Allograft versus autograft osteochondral transplant for chondral defects of the talus: systematic review and meta-analysis. Am J Sports Med 2022;50(12):3447–55.
36. Kennedy JG, Murawski CD. The treatment of osteochondral lesions of the talus with autologous osteochondral transplantation and bone marrow aspirate concentrate: surgical technique. Cartilage 2011;2(4):327–36.
37. Nguyen A, Ramasamy A, Walsh M, et al. Autologous osteochondral transplantation for large osteochondral lesions of the talus is a viable option in an athletic population. Am J Sports Med 2019; 47(14):3429–35.
38. Everts P, Onishi K, Jayaram P, et al. Platelet-rich plasma: new performance understandings and

therapeutic considerations in 2020. Int J Mol Sci 2020;21(20). https://doi.org/10.3390/ijms21207794.
39. Danilkowicz RM, Grimm NL, Zhang GX, et al. Impact of early weightbearing after ankle arthroscopy and bone marrow stimulation for osteochondral lesions of the talus. Orthop J Sports Med 2021;9(9). 23259671211029883.
40. Görmeli G, Karakaplan M, Görmeli CA, et al. Clinical effects of platelet-rich plasma and hyaluronic acid as an additional therapy for talar osteochondral lesions treated with microfracture surgery: a prospective randomized clinical trial. Foot Ankle Int 2015;36(8):891–900.
41. Guney A, Akar M, Karaman I, et al. Clinical outcomes of platelet rich plasma (PRP) as an adjunct to microfracture surgery in osteochondral lesions of the talus. Knee Surg Sports Traumatol Arthrosc 2015;23(8):2384–9.
42. Seow D, Ubillus HA, Azam MT, et al. Limited evidence of adjuvant biologics with bone marrow stimulation for the treatment of osteochondral lesion of the talus: a systematic review. Knee Surg Sports Traumatol Arthrosc 2022. https://doi.org/10.1007/s00167-022-07130-z.
43. Boakye LA, Ross KA, Pinski JM, et al. Platelet-rich plasma increases transforming growth factor-beta1 expression at graft-host interface following autologous osteochondral transplantation in a rabbit model. World J Orthop 2015;6(11):961–9.
44. Smyth NA, Haleem AM, Murawski CD, et al. The effect of platelet-rich plasma on autologous osteochondral transplantation: an in vivo rabbit model. J Bone Joint Surg Am 2013;95(24):2185–93.
45. Russell RP, Apostolakos J, Hirose T, et al. Variability of platelet-rich plasma preparations. Sports Med Arthrosc Rev 2013;21(4):186–90.
46. Caplan AI. Mesenchymal stem cells. J Orthop Res 1991;9(5):641–50.
47. Fortier LA, Strauss EJ, Shepard DO, et al. Biological effects of bone marrow concentrate in knee pathologies. J Knee Surg 2019;32(1):2–8.
48. Barry F, Boynton RE, Liu B, et al. Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components. Exp Cell Res 2001;268(2):189–200.
49. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J Bone Joint Surg Am 2010;92(10):1927–37.
50. Wilke MM, Nydam DV, Nixon AJ. Enhanced early chondrogenesis in articular defects following arthroscopic mesenchymal stem cell implantation in an equine model. J Orthop Res 2007;25(7):913–25.
51. Murphy EP, McGoldrick NP, Curtin M, et al. A prospective evaluation of bone marrow aspirate concentrate and microfracture in the treatment of osteochondral lesions of the talus. Foot Ankle Surg 2019;25(4):441–8.
52. Mercer NP, Samsonov AP, Dankert JF, et al. Outcomes of autologous osteochondral transplantation with and without extracellular matrix cartilage allograft augmentation for osteochondral lesions of the talus. Am J Sports Med 2022;50(1):162–9.
53. Shimozono Y, Yasui Y, Hurley ET, et al. Concentrated bone marrow aspirate may decrease postoperative cyst occurrence rate in autologous osteochondral transplantation for osteochondral lesions of the talus. Arthroscopy 2019;35(1):99–105.
54. Doral MN, Bilge O, Batmaz G, et al. Treatment of osteochondral lesions of the talus with microfracture technique and postoperative hyaluronan injection. Knee Surg Sports Traumatol Arthrosc 2012;20(7):1398–403.
55. Kaplan LD, Lu Y, Snitzer J, et al. The effect of early hyaluronic acid delivery on the development of an acute articular cartilage lesion in a sheep model. Am J Sports Med 2009;37(12):2323–7.
56. Bajuri MY, Sabri S, Mazli N, et al. Osteochondral injury of the talus treated with cell-free hyaluronic acid-based scaffold (Hyalofast®) - a reliable solution. Cureus 2021;13(9):e17928.
57. Tahta M, Akkaya M, Gursoy S, et al. Arthroscopic treatment of osteochondral lesions of the talus: Nanofracture versus hyaluronic acid-based cell-free scaffold with concentration of autologous bone marrow aspirate. J Orthop Surg (Hong Kong) 2017;25(2). 2309499017717870.
58. Yontar NS, Aslan L, Can A, et al. One step treatment of talus osteochondral lesions with microfracture and cell free hyaluronic acid based scaffold combination. Acta Orthop Traumatol Turc 2019;53(5):372–5.
59. Colasanti CA, Mercer NP, Garcia JV, et al. In-office needle arthroscopy for the treatment of anterior ankle impingement yields high patient satisfaction with high rates of return to work and sport. Arthroscopy 2022;38(4):1302–11.