REVIEW

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Orthobiologic Injectables in the Ankle Joint: a Narrative Review

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SUMMARY

Background. The ankle joint is a frequent site of injury and bone remodeling, and often requires cartilage repair. Studies have shown that growth factors and bioactive compounds have regenerative properties capable of promoting cartilage restoration. Hyaluronic acid (HA) and orthobiologics like platelet-rich plasma (PRP) and adult stem cells (ASCs) are particularly interesting as therapeutic solutions for ankle cartilage repair and have received considerable attention over the years.

Methods. We performed a literature review to summarize the clinical uses and outcomes of HA, PRP and ASCs as reparative interventions in osteochondral lesions (OCL) and osteoarthritis (OA) of the ankle, when used alone and post-surgically.

Results. In total, 50 studies were eligible and included in this review. HA was shown to be a safe treatment option with a low rate of adverse effects and overall clinical improvement for talar OCL when used alone and post-surgically. PRP was found to be superior to HA for talar OCL in non-surgical and post-surgical patients. Studies evaluating HA injections for ankle OA noted a general improvement in pain and function post-injection with minimal adverse reactions, though there is mixed data regarding the efficacy of PRP injections for ankle OA. High-level randomized controlled trials are lacking for the evaluation of ASCs in talar OCL and ankle OA, though limited research has found them to be safe and efficacious.

Conclusions. HA and orthobiologics can be considered for use as a pre-surgical treatment in ankle OCL and OA, or as a second-line treatment for patients who remain symptomatic after surgery. The safety profile and subjective improvement in clinical outcomes following orthobiologic treatments is promising, though requires additional investigation.

KEY WORDS

Adult stem cells; ankle osteoarthritis; BMAC; hyaluronic acid; mesenchymal stem cells; MFAT; platelet-rich plasma; talar osteochondral lesions.

BACKGROUND

Osteochondral lesions and osteoarthritis of the ankle

The use of viscosupplementation and orthobiologic therapies to aid in cartilage tissue repair in osteochondral lesions (OCLs) and osteoarthritis (OA) of the ankle has received noteworthy attention (1-4). Articular cartilage disease is primarily a disease of hyaline cartilage, chondrocytes, and is commonly caused by injury and degeneration. Because articular cartilage is largely avascular and has a low number of chondrocytes, the regenerative capacity of the joint is

limited, and regeneration-stimulating therapies would be beneficial (5).

Intra-articular damage of the ankle is commonly associated with talar OCLs, which involve injuries of the articular surface of the talar dome and the underlying subchondral bone (6). Common causes for ankle OCLs include trauma, necrosis, embolism, alcohol abuse, metabolic diseases, ligament instabilities and hereditary disorders (7, 8). Talar OCL is common in athletes, especially those with chronic ankle instability, and occurs in 70% of all ankle sprains and fractures (9-11). The presentation of talar OCL includes pain upon weight bearing, a reduction of range of motion, stiffness, functional impairment, instability, swelling and mechanical symptoms such as clicking, catching and locking (12). Treatment options for OCLs include surgical procedures like arthroscopic debridement, chondrocyte transplantation, and arthrotomy, as well as nonsurgical techniques including cast immobilization and intra-articular injections (13-20).

OA is a common degenerative joint disease and ankle OA comprises approximately 13% of all OA cases (21-23). While primary ankle OA is less common, the incidence of posttraumatic and inflammatory ankle OA is on the rise (23). The underlying mechanism of OA is complex and depends on a variety of factors (24-26). The major characteristics and consequences of ankle OA include joint pain, decreased quality of life, limitations in activities of daily living, articular cartilage degeneration, chondrocyte loss, bone remodeling, limited movement, joint effusion, and (systemic) inflammation (5, 27, 28). Joint movement requires smooth motion and minimal friction of bones provided by hyaline cartilage, comprised primarily of chondrocytes (5). Although a number of nonsurgical therapies like analgesics and physical therapy may be effective in mitigating symptoms and improving function in ankle OA, they also have adverse effects and may only provide temporary relief (29). Nonsurgical interventions are commonly considered for patients who are not surgical candidates or who prefer to delay surgery.

The outcomes of surgical and non-surgical treatment options for ankle joint disease can vary. In addition to viscosupplementation or hyaluronic acid (HA), the use of platelet-rich plasma (PRP), and adult stem cells (ASCs) including mesenchymal stem cells and amniotic stem cells as regenerative therapies for these injuries and degenerative conditions is steadily increasing (22, 30-32). The purpose of this review is to provide a comprehensive overview of the clinical outcomes of the utilization of viscosupplementation and orthobiologics in ankle OCL and OA. We will review and summarize the existing surgical and injectable treatment options for tibiotalar joint disease. We will focus on a critical review of the existing scientific literature investigating the use and clinical outcomes of HA, PRP and ASCs in the treatment of ankle OCL and OA.

Surgical ankle procedures

Surgical procedures in ankle lesions aimed at cartilage regeneration include palliative (chondroplasty, debridement), reparative (microfracture [MF], drilling), and restorative procedures (autologous chondrocyte implantation [ACI], autologous osteochondral transplantation [AOT]) (33-35). These treatments have varying success rates, can be costly, and sometimes require repeat surgeries (20). Of these techniques, arthroscopic MF surgery is frequently offered as a first-line surgical treatment option for OCLs as it is less invasive, has lower complication risks, and is relatively inexpensive (9, 36). In MF, small drill holes are created in the subchondral bone, exposing the deeper and more vascularized portion of the bone to the joint surface. MSCs from the deeper bone layer travel to the surface layer, respond to local growth factor signaling, and contribute to fibrocartilaginous differentiation and cartilage growth. MF can be performed in small- to medium-sized cartilage defects. Approximately 30% of all MF surgery shows poor results at follow-up, including lack of infill at the defect, formation of fibrocartilage instead of hyaline cartilage, worsening arthritis grade, persistent pain, and poor return to activity (37-40).

Techniques like osteochondral autografting (mosaicplasty), osteochondral allografts and ACI have also been used for OCL treatment (41-43). Mosaicplasty involves the use of cylindrical osteochondral autografts and aims to reconstruct the articular surface so as to closely resemble healthy joints (44-48). ACI was developed to allow differentiated chondrocytes, bioabsorbable hyaluronan scaffolds (49), or collagen (50, 51) to promote hyaline cartilage synthesis.

Nonsurgical ankle treatments: viscosupplements and orthobiologics

Hyaluronic acid

Cartilage degeneration is characterized by loss of type II collagen and glycosaminoglycans like HA, present in the synovial fluid and cartilage, and of chondroitin sulfate, present in the cartilage matrix. HA is an essential component of the joint where it provides viscosity and elasticity to the synovial fluid (52, 53). It also functions as a shock absorbent, has analgesic and anti-inflammatory effects, and protects the joint and soft tissues during activity (54). When HA is depleted, cartilage degradation is accelerated. Intra-articular HA injections have been widely used for joint diseases

during the past decades with studies demonstrating mixed outcomes. Clinically beneficial effects may include restoration of joint function and decreased pain (55-58). While HA injections do not appear to replicate all the properties of endogenous HA, injections may provide relief via anti-inflammation and by maintaining viscoelasticity (59).

Platelet-rich plasma

PRP is composed of platelets, growth factors, and cytokines and prepared by isolating these released activated products after centrifugation of autologous venous blood. There is evidence that PRP injection contributes to cartilage regeneration (60), as platelets play an important role in wound healing through cytokines like transforming growth factors-beta (TGF-β) (61). TGF-β coordinates the migration of bone-marrow stromal cells, which aid in the induction of chondrocyte differentiation and expansion (62). Laboratory studies have shown that PRP can induce cell proliferation and cartilaginous matrix production and is safe to treat musculoskeletal injuries. Consequently, clinical studies of PRPs in OCL and OA in multiple joints are steadily increasing (63-69).

Adult stem cells: medicinal signaling cells

ASCs are capable of self-renewal and may differentiate into cells like adipocytes, chondroblasts, and osteoblasts (70). These stem cells are the proposed adult stem cells present in bone marrow aspirate concentrate (BMAC), microfragmented adipose tissue (MFAT), adipose-derived stem cells (ADSCs), amniotic stem cells (AmSCs), and umbilical cord stem cells (UCSCs) and all have the potential to promote cartilage repair (71).

BMAC is harvested from bone marrow and consists of mesenchymal stem cells (MSCs), hematopoietic stem cells, and growth factors. The rationale for its use is that BMAC facilitates tissue regeneration and increases aggrecan production and as such cartilage quality (70), while also minimizing the formation of fibrocartilage (73-75). Adding BMAC to bone marrow stimulation (BMS) procedures has revealed significant improvements over BMS alone, showing cartilage with higher hyaline content and more glycosaminoglycans (76, 77).

MFAT is obtained by microfragmenting aspirated autologous fat tissue, resulting in an end product that contains microvessels and pericytes (78, 79). Pericytes give rise to MSCs (known as ADSCs) capable of enhancing tissue regeneration at the site of injection (80, 81). MFAT is furthermore rich in angiogenic, anti-inflammatory, and immunomodulatory growth factors and cytokines (78, 79).

Amniotic stem cells and umbilical cord cells have been shown to contain ASCs as well (82). Human AmSCs containing ASCs were shown to secrete exosomes with growth factors and were effective in attenuating disease progression in animal models of rheumatoid arthritis (83), osteoarthritis (84), and bone defects (85).

MATERIALS AND METHODS

Inclusion of relevant published scientific studies

We conducted a comprehensive narrative review using existing literature, describing the clinical outcomes of HA, PRP, and ASCs (BMAC, ADSCs, AmSCs, UCSCs) for the treatment of OCL and OA of the ankle. We focused on clinical research articles published up until April 2020 from database searches using the electronic databases PubMed/MEDLINE, and the Cochrane Library. The literature searches we used included the search terms shown in **table I**. Eligibility, inclusion and exclusion criteria are summarized in **table I** and were screened by MSR and EYR. Our literature search identified a total of 155 publications, of which 50 were eligible and included in this review. The primary clinical outcomes are described in **tables III** to **VIII** and include pain and function scores and imaging evaluation. Abbreviations used throughout these tables are listed in **table II**.

Table I. Search terms used for databases, inclusion/exclusion criteria, and level of evidence.

Search terms for inclusion in systematic review	Used for review
Ankle osteochondral lesions AND hyaluronic acid	3
Ankle osteochondral lesions AND platelet-rich plasma	6
Ankle osteochondral lesions AND bone marrow OR mesenchymal stem cells OR amniotic stem cells OR adipose stem cells OR adult stem cells	14
Ankle osteoarthritis AND hyaluronic acid	19
Ankle osteoarthritis AND platelet-rich plasma	4

Search terms for inclusion in systematic review	Used for review
Ankle osteoarthritis AND bone marrow OR mesenchymal stem cells OR amniotic stem cells OR adipose stem cells OR adults stem cells	4
Inclusion criteria	English-language research publications Original articles (no reviews) Clinical studies (all Levels) Subjects with diagnosed ankle OCL or ankle OA. Interventions with HA, PRP, or ASCs with or without surgery
Exclusion criteria	Non-English research publication Animal studies, *in vitro or in vivo* studies Pathology other than ankle OCL or ankle OA Primary affected joint was not the ankle
Level of Evidence	
Level I	Prospective randomized clinical trial (RCT) Meta-analysis of RCT with homogeneous results
Level II	Prospective comparative study Meta-analysis of Level 2 studies or Level 1 studies
Level III	Retrospective case-control study Case-control study Meta-analysis of Level 3 studies
Level IV	Case series
Level V	Expert opinion Case Report Personal Observation

RESULTS

We found 23 studies involving ankle OCLs (3 HA, 6 PRP, and 14 ASC studies; **tables III-V**), and 27 studies involving osteoarthritis of the ankle (19 HA, 3 PRP and 4 ASC studies; **tables VI-VIII**) that matched our inclusion criteria.

Hyaluronic acid for the treatment of osteochondral lesions of the ankle

Our search revealed three published reports eligible for inclusion, including one prospective clinical trial (level of evidence I), and two prospective case series (level of evidence II). One study analyzed the treatment of intra-articular HA injections, and two studies compared MF only *versus* MF combined with postoperative HA injections (**table III**).

Mei-Dan and colleagues (2008) determined the effects of HA injection in talar OCL and revealed decreased VAS scores for pain, stiffness and improved function within 12 weeks following the injection, lasting up to 26 weeks (86).

Arthroscopic debridement and MF with and without post-operative intra-articular HA injections were studied by two groups (87, 88). MF surgery was shown to improve post-operative functionality and pain scores, confirming previous reports, and postoperative HA injections significantly amplified these clinical outcomes for up to 2 years

Table II. Abbreviations.

Frequently used scoring systems
AHFS: Ankle/Hindfoot Score
AOFAS: American Orthopedic Foot and Ankle Society
AOS: Ankle Osteoarthritis Scale
EQ-5D: EuroQol
FAAM: Foot and Ankle Ability Measure
FADI: Foot and Ankle Disability Index
FAOS: Foot and Ankle Outcome Score
ICRS grade: International Cartilage Repair Society grade
JSSF: Japanese Society for Surgery of the Foot
MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue
MOS: Medical Outcomes Study
SAFE-Q: Self-Administered Foot Evaluation Questionnaire
SF12: 12-item Short Form Survey

Frequently used scoring systems
SF-36: Medical Outcomes Study, short form, 36-item survey
sGFS: Subjective global function score
SLS: Single Leg Stance test
TAS: Tibial Ankle Surface
TLS: Tibial Lateral Surface
TT: Talar Tilt
TUG: Timed 'Up-and-Go' test
VAS: Visual Analog Scale
VAS-FA: Visual Analog Scale for Foot and Ankle
WOMAC: Western Ontario and McMaster Universities OA Index
Commonly Used Terms
ACI: Autologous Chondrocyte Implantation
ADSC: Adipose-Derived Stem Cell
AE: Adverse Effects
AmSC: Amniotic Stem Cell
AOT: Autologous Osteochondral Transplantation
ASC: Adult Stem Cell
BMAC: Bone Marrow Aspirate Concentrate
BME: Bone Marrow Edema
BMS: Bone Marrow Stimulation
CS: Case Series
HA: Hyaluronic Acid
MFAT: Microfragmented Adipose Tissue
MSCs: Mesenchymal Stem Cells
OA: Osteoarthritis
OCL: Osteochondral Lesions
PC: Prospective Cohort
PCS: Prospective Case Series
PJAC: Particulated Juvenile Articular Cartilage
PRCT: Prospective Randomized Controlled Trial
PRGF: Plasma rich in growth factors
PRP: Platelet-Rich Plasma
QoL: Quality of Life
RCS: Retrospective Case Series
RCSt: Retrospective Cohort Study
RCT: Randomized Controlled Trial
RCT-DB: Randomized Controlled Trial Double Blind
ROM: Range of Motion
UCSC: Umbilical Cord Stem Cell

(89, 90). Using quantitative MRI, the cartilage thickness index was increased and the T2 value was decreased in the MF with injection group which is suggestive of chondrogenic potentiation and decreased inflammation (88). The absence of major complications such as neurovascular injury, infections, stiffness or thrombotic events lends support to combining surgery and HA injections.

In summary, our study analysis revealed that intra-articular HA injections for talar OCL decrease pain and improve ankle function. While MF surgery by itself improved pain and function, adding HA injections after MF provided better clinical outcomes.

Platelet-rich plasma for the treatment of osteochondral lesions of the ankle

One of the six studies included in this review was a level I study, four were level II and one was level III (**table IV**). Two studies investigated the benefit of injections without surgery (91, 92), and the remaining four studies focused on the combination of surgery, such as MF or autograft, with intra-articular PRP injections (93-95), or a bone autograft surgery with a PRP scaffold instead of an injection (96).

Intra-articular injections of either PRP or HA without any surgery was shown to improve ankle function and decrease pain for at least 6 months (91). Interestingly, PRP was found to be more effective than HA in improving ankle function and in decreasing pain and stiffness. The clinical improvements in both PRP and HA therapies occurred primarily during the first 12 weeks. After 12 weeks, PRP continued to improve ankle function and pain, whereas for HA, the improvements declined after 28 weeks. Similarly, the effects of either PRP or HA adjunct to arthroscopic debridement and MF surgery improved pain and function, with a superior effect for PRP (93).

Akpancar and Gul (2019) compared 2 types of intra-articular and tibial edge/talar dome injections: PRP and prolotherapy (PrT) (92). For intra-articular prolotherapy injection, the authors injected 2 ml 25% dextrose intra-articularly and 1.8 ml 15% dextrose in combination with 0.2 ml lidocaine. Both PRP and PrT improved pain and function to 1 year without significant side effects, supporting the use of either PRP or PrT in talar OCL.

Guney and co-workers reported that mosaicplasty was most effective in decreasing ankle pain from talar OCL (94, 95). Applying a PRP scaffold with a cancellous bone autograft in talar OCL (Hepple stage V) also revealed that PRP enhances the healing of articular cartilage injuries and improves ankle function (96).

In summary, these results indicate that for talar OCL, intra-articular PRP injections improve ankle joint function-

Table III. HA in osteochondral lesions of the ankle.

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Mei-Dan *et al*., 2008: Efficacy of HA in pain reduction in talar OCL	-PCS -Level: II -n = 16, but 15 analyzed, three weekly injections of intra-articular HA	Injection: Intra-articular injection of HA - Follow-up: up to 26 wks	-VAS -AOFAS -AHFS -sGFS	-Mean VAS decreased for pain, stiffness and function by week 26. -sGFS (0-100) improved by week 26	Talar OCD treated with intra-articular HA injections decreases pain and increases ankle function within 12 wks
Doral *et al*., 2012: -Outcome of MF surgery with or without postoperative intra-articular HA injections in talar OCL	-PRCT -Level: I -total of 57 patients, surgery with adjunct intra-articular HA injections (n = 41) *vs* surgery only (n = 16)	Surgery alone *vs* surgery with injection: MF surgery with or without 3 postoperative intra-articular HA injections. -Follow-up: 2 years	-Freiburg score -AOFAS -AHFS	-Improved Freiburg and AOFAS scores in both groups compared to preoperative findings. -Better clinical outcomes in the surgery with injection group than surgery alone group	Talar OCL treatment with MFimproves postoperative functionality and pain scores, enhanced further by adjunct intra-articular HA injections
Shang *et al*., 2016: Comparison of clinical and MRI outcomes following MF surgery alone or with HA in talar OCL treatment	-PCS -Level: II -n = 35 (MF, n = 17; intra-articular HA injection post-op, n = 18)	Surgery alone *vs* surgery with injecton: MF with or without intra-art HA injection. (1 week interval, 3 in total: intra-op, 1 week and 2 post-op) -Follow-up: at least 9 mos	-qMRI (to evaluate postoperative cartilage repair) -AOFAS -AHFS -VAS	MRI outcomes: Surgery + injection group showed higher thickness index but lower T2 index -AOFAS and VAS were improved in Surgery + injection group	MF surgery in combination with adjunct intra-articular HA injections improves functional recovery compared to surgery alone

ality and pain symptoms more than HA injections. Additionally, the use of PRP injections alongside MF surgery improved clinical outcome more than treatment with MF surgery with HA, or with MF surgery alone. Non-operative treatment with PRP seems to be an efficacious and safe orthobiologic treatment, especially when surgery is contraindicated. However, more long-term studies with an increased sample size are required to determine the role of these findings in current treatment guidelines.

Adult stem cells for the treatment of osteochondral lesions of the ankle

We found 14 publications focused on the role of ASC therapy in talar OCL eligible for review inclusion. The majority of the 14 ASC studies were case series and cohort studies (level of evidence III and IV). All 14 reports were based on surgical procedures, of which 9 studied the implantation of bone marrow-derived MSCs or BMAC, three investigated surgeries combined with MFAT or adipose-derived MSC injections, one studied the addition of umbilical cord allografts, and one studied AmSCs (**table V**). There was no study focusing on nonsurgical injection-only ASC treatments.

Several studies reported that one-step arthroscopic implantation of BM-derived MSCs on a supportive scaffold (collagen powder or HA) could improve ankle function in talar OCL (15, 97, 98) and could regenerate cartilaginous tissue by the arthroscopy (99). Giannini *et al*. (2009) reported that arthroscopic BM-derived scaffold implantation results in functional improvement similar to other surgical techniques like chondroplasty, MF, and ACI (15, 89, 100, 101). However, the one-step method described by Giannini and colleagues (2009) was significantly less invasive. JACI-BMAC therapy yielded no significant improvement in VAS scores and resulted in fibrocartilage tissue instead of normal cartilage tissue (102). Arthroscopic implantation of matrix-induced BMAC on periosteal or HA scaffolds seemed inferior to matrix-induced ACI, which showed better AOFAS scores (103), even though cartilage repair was comparable in both groups.

Table IV. PRP in osteochondral lesions of the ankle.

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Mei-Dan *et al.*, 2012: Safety and efficacy of PRP *vs* HA in talar OCL	-PCS -Level: II -N = 30: 15 HA and 15 PRP patients) -Inclusion: patients who failed to respond to non-operative treatment -PRP in PRGF	Injection: -intra-articular PRP or HA injection -Follow-up: 28 wks	-Function, ROM, AE, swelling at wks 4, 12, 28 post-injection -AHFS and VAS (pain, stiffness, function) -Subjective global function score (sGFS; 0-100)	-AHFS improved from 66 to 78 (HA) and 92 (PRP) -Mean VAS decreased for pain, stiffness, and function -sGFS improved from 56 to 73 (HA) and 58 to 91 (PRP) by week 28	-HA and PRP treatments in ankle OCL decrease pain and improve function for at least 6 mo. -minimal AE -PRP is more effective than HA in symptom improvement
Görmeli *et al.*, 2015: Effects of adjunct PRP or HA injections following MF surgery	-PRCT -Level: I -N = 40 (13 PRP, 14 HA, 13 saline) -PRP prep: Smart PRePR2	Surgery and injection: -MF surgery and adjunct injections of PRP, HA or saline control - Follow-up: 11-25 mos (mean 15.3 mos)	-AOFAS -VAS	-Significantly increased AOFAS: PRP>HA>saline -VAS: PRP (Lower)< HA<control	Adjunct PRP or HA with talar OCL MF surgery improved clinical outcomes
Guney *et al.*, 2015: Clinical outcomes of adjunct PRP treatment with talar OCL surgery	- PCS - Level: II - n = 35 (n = 19 PRP and surgery; n = 16 surgery alone) -PRP prep: Smart PRePR2	Surgery, injection or both: -MF surgery and adjunct injections of PRP *vs* surgery alone -Follow-up 12-24 mo (mean 16.2 mo)	-AOFAS -FAAM -VAS	-AOFAS and FAAM were similar in both groups. -VAS was decreased and a better outcome was seen in the combination group *vs* surgery alone	MF surgery combined with PRP injections in talar OCL improves medium-term outcome
Guney *et al.*, 2016: Compare medium-term effects of MF surgery, MF surgery plus PRP, and mosaicplasty	-PCS -Level: II -n = 54 (MF surgery n = 19, MF surgery plus PRP n = 22, mosaicplasty n = 13) -PRP prep: Smart PRePR2	Surgery alone or with injection: -MF surgery, with or without arthroscopic inj PRP *vs* mosaicplasty -Follow-up 12-84 mos (mean 42 mos)	-AOFAS -VAS -FAAM pain -FAAM 15 min walking	-All 3 groups showed significant improvements in in AOFAS and VAS -VAS improvement was superior in mosaicplasty	All treatment options revealed good outcomes, but mosaicplasty seems more promising, especially in pain control
Gu *et al.*, 2017: clinical outcome of bone autograft and PRP scaffolds in Hepple V talar OCL	-PCS - Level: II -N = 14 (13 analyzed) -PRP prep: WEGO PRP kit	Surgery: Application of cancellous bone autograft and PRP scaffold -Follow-up: 11-48 mos (mean 23.5 mos)	-Ankle X-ray/MRI -VAS -AOFAS -SF-36 -ROM ankle	-Complete regeneration of bone and cartilage -VAS, AOFAS and SF-36 improved	For Hepple stage V talar OLC, cancellous bone autograft and PRP scaffold therapy seems safe and effective
Akpancar & Gul, 2019: Comparison of PRP and PrT injections in talar OCL	-RCSt (cohort) - Level: III -N = 49 (PrT n = 27, PRP n = 22) -PRP prep: GPS III	Injection: -Intra-articular injections (PRP or PrT) -Follow-up: baseline, 21d, 90d, 180d, 360d	-VAS -AOFAS -AOS	Both PRP and PrT improved ankle function up to 1 yr with comparable efficacy	PRP and PrT are equally efficient and safe in the treatment of talar OCL

The BMAC-treated group also showed increased expression of fibrous markers and the hypertrophy marker Collagen X (103). Midterm results involving AOT revealed that the addition of BMAC and collagen matrix can enhance the integration of bone (74, 104). Lanham and colleagues investigated the clinical outcome of particulated juvenile articular cartilage (PJAC) compared to BMAC scaffolds (105). Although the initial results seem to be in favor of PJAC, the small sample size and potential dissimilar lesion sizes warrants further investigation.

Kim *et al.* (2013, 2014) reported that the use of ADSCs or MFAT together with MF resulted in a better functional outcome than MF alone (106, 107). Of note, the authors also concluded that larger lesions and subchondral cysts respond better to the addition of ASCs. The use of MFAT in the management of talar OCL revealed clinical improvement without complications, albeit the sample size was small (n = 4) (108). MF surgery combined with arthroscopic BMAC also seemed to decrease revision rates in ankle OCL, with similar effects on pain and function scores (109).

The addition of amniotic allografts to arthroscopy and MF for talar dome lesions smaller than 2 cm^2 resulted in significantly improved function and pain scores in early and late follow-up stages with no adverse effects (**table V**) (110). A pilot study showed that umbilical cord allografts combined with arthroscopy for the treatment of talar OCL can reduce OCL size as well, allowing room for future studies with a larger patient volume (111).

Based on current findings, BMAC has a beneficial effect on OCL repair and overall improvement in ankle function. Marrow stimulation in combination with BMAC injection improved clinical outcomes more than marrow stimulation alone. BMAC as a therapy is well tolerated and decreases revision rates, but ACI seems to provide more favorable AOFAS scores. In addition, the use of MFAT, amniotic allografts and umbilical cord tissue as adjuncts to surgery were found to be safe and promising.

Hyaluronic acid for the treatment of ankle osteoarthritis

The use of HA in ankle OA was reported in 19 eligible publications, of which six were clinical trials (level I), eight were prospective case series (level II), and the remaining studies were level III or IV studies (**table VI**).

The overall clinical outcome for intra-articular HA injections seems to be positive, with decreased pain, improved function and minimal adverse effects when given as the primary intervention (112-118), when compared to control saline injections (119), or when given following arthroscopic procedures (24). Giving one intra-articular HA injection resulted in pain relief and improved ankle function (117, 118), as did five weekly injections without surgery (112, 113) and three weekly HA injections combined with arthroscopy (24). Compared to saline, the beneficial effects of HA injections lasted at least 3 months (119). Despite the fact that the difference was not as significant after 6 months, the patients still reported a clear improvement compared to baseline. Other groups found that intra-articular HA injections improved VAS scores up to 6 months (115) and AOS scores up to 18 months (114). It has also been demonstrated that three weekly 1 ml HA injections were more effective in reducing pain (21, 120) than single 1 ml, 2 ml, or 3 ml injections (120). Early-stage OA was associated with improved VAS scores and higher satisfaction rates, emphasizing the importance of the proper inclusion of OA grade (121).

However, no significant difference was found between HA and saline injections in ankle OA in pain and function after 12 weeks (122) or in the clinical outcome between HA injections and exercise alone (123). Both botulinum toxin injections and HA injections combined with exercise improved pain and function without statistical differences between the two groups (124). Despite the mixed outcomes, most studies analyzed here were in favor of using intra-articular HA injection for ankle OA with minimal risks.

Platelet-rich plasma for the treatment of ankle osteoarthritis

We found four publications reporting PRP use in ankle OA that were eligible for inclusion, two of which were retrospective case studies (level of evidence III) (125, 126), one prospective case series (level of evidence IV) (22), and one double-blinded randomized clinical trial (level of evidence I) (127). All four studies reported the results of intra-articular PRP injection.

Angthong and colleagues analyzed the clinical improvement and quality of life outcomes in various foot and ankle disorders, including four patients with ankle OA Takakura stage I-IIIb (125). All patients were treated with fluoroscopic or ultrasound guided leukocyte poor PRP injections. PRP injections were found to be safe and improved VAS and SF-36 scores (22, 125, 126). These studies support the possibility of delaying surgical treatment, especially in younger patients. Taken together, current case studies indicate that PRP injections are generally safe for the treatment of ankle OA.

Paget and colleagues (2021) performed a randomized clinical trial in 100 patients with ankle OA comparing treatment with two intraarticular PRP injections *versus* placebo saline injections. The authors found no difference in mean change in AOFAS over 26 weeks between groups, and noted no significant adverse events related to the injections (127).

Table V. ASCs and osteochondral lesions of the ankle.

Study	Model	Treatment	ASC prep	Outcome measures and Scores	Results	Conclusion
Giannini *et al.*, 2009: BM-derived cells on scaffolds for talar OCL repair	-PCS -Level: IV -n = 48	Surgery: -Arthroscopic implantation of BM-derived cell scaffold -Follow-up: 24-35 mos (mean 29 mos)	Porcine collagen powder or HYAF-11 with platelet gel. Cell viability by: MTT (Mossman)	-AOFAS -MRI -Histology	- improved AOFAS -histology: regeneration of tissue, but none showed entirely hyaline cartilage	Implantation of BM-derived cells improves ankle functionality in talar OCL treatment
Kennedy and Murawski, 2011: Autologous OC transplantation with BMAC	-Cohort study -Level: III -n = 72	Surgery: -AOT with BMAC - Follow-up: 12-64 mo (mean 28.02 mos)	BMAC centrifuge	-AOFAS -SF12	Both AOFAS and SF12 improved	Autologous OC transplantation is a reproducible treatment strategy for large talar OCL
Buda *et al.*, 2013: Efficacy of scaffold supported BM-derived cells in talar OCL repair	-Case series -Level: IV -n = 64	Surgery: -Arthroscopic cartilage repair using BM-derived cell collagen or HA membrane scaffold - Follow-up: aimed at 6, 12, 18, 24, 36, 42, 60, 72 mos (mean 53 mos)	Porcine collagen powder or hyaluronic acid membrane	-AOFAS	AOFAS improved (65.2 to 80)	Using BM-derived cells supported by scaffolds significantly improved talar OCL
Kim *et al.*, 2013: Compare the outcome of arthroscopic marrow stimulation alone, or with MFAT injections in talar OCL	-Cohort study -Level: III -n = 65 (marrow, n = 35; MFAT and marrow, n = 30) -Inclusion: 50 yr+ patients	Surgery alone or with injection: -Arthroscopic marrow stimulation with and without the injection of MFAT -Follow-up: 12-44 mos (mean 21.8 mos)	MSCs: collagenase treatment, centrifugation	-VAS -AOFAS -Roles and Maudsley -Tegner activity scale	-VAS and AOFAS improved in both. -Roles and Maudsly sign improved in MFAT/marrow *vs* marrow alone. -Tegner scale was significantly improved in MFAT/marrow	MFAT injections combined with arthroscopic marrow stimulation in 50yr+ patients seem superior to BMS alone

Study	Model	Treatment	ASC prep	Outcome measures and Scores	Results	Conclusion	
Kim *et al.*, 2014: Compare clinical and MRI outcomes in adipose-derived MSC inj with arthroscop marrow stim *vs* marrow stim alone in talar OCL	-cohort study -Level: III -n = 49 (marrow stim/ MSC n = 24; marrow stim, n = 26)	Surgery alone or with injection: -Arthroscopic marrow stimulation alone of with injection of adipose-derived MSCs -Follow up: 16-25 mos (mean 21.9 mos)	Adipose cell: centrifugation separation. Culture in adipogenic induction medium, or osteogenic medium or chondrogenic medium (containing eg dexamethasone, B-glycerol phosphate)	-VAS -AOFAS -Tegner activity scale -MOCART	VAS, AOFAS and Tegner had improved in both groups, but more for MSC + marrow compared to marrow only. -Worse MOCART score in marrow only group	In the treatment of talar OCL, adipose-derived MSCs with marrow stimulation improves clinical and MRI outcomes more than marrow stimulation alone
Anderson and Swayze. 2015: Arthroscopy and MF of talar OCL (lesion <2 cm^2) with and without amniotic allograft	-C -Level:II -n = 101 (54 with graft, 47 without)	Surgery: Arthroscopy and MF with or without amniotic allograft -Follow-up: up to 24 mos	Human amniotic allograft (cryopreserved liquid form)	-ACFAS (pre-op, 3, 12, 24 mos) -VAS (pre-op and 24 mos)	-Significant improvement in both groups -Amniotic graft significantly better outcome (early and up to 24 mos) - No AE	Combining talar OCL arthroscopy, MF, and amniotic allograft in talar dome lesions <2 cm^2 significantly improve pain and function scores
Lanham *et al.* 2016: Evaluating the outcomes of iliac crest BMAC collagen scaffold *vs* PJAC for talar OCL treatment	-RCS -Level: IV -n = 12	Surgery: -Iliac crest BMAC collagen scaffold *vs* PJAC - Follow-up: 12-42 mos (mean 25.7 mos)	BMAC: centrifuge, mixed with hydrated matrix scaffold (bovine collagen and glycosaminoglycan)	-AOFAS -FAAM -SF12	-AOFAS, FAAM and SF12 all improved more in PJAC than in BMAC scaffolds treatments	PJAC showed a superior clinical outcome compared to BMAC scaffold treatments
Sadlik *et al.* 2016: Autologous bone chips with BMAC and fibrin, xenogeneic collagen membrane in large talar OCL to restore talus convexity	-Cohort study -Level: III -Midterm results -n = 10	Surgery: Autologous bone chips with BMAC and fibrin, and xenogeneic collagen membrane - Follow-up: 46 mos (+/- 18 mos)	BMAC: BMS, centrifugation and separation	-AOFAS -VAS -MOCART	-AOFAS improved after treatment -VAS decreased -MOCART averaged at 69.5%	Autologous bone chips with BMAC and fibrin, xenogeneic collagen membrane recreates convexity and curvature of the large OCL talar dome

Study	Model	Treatment	ASC prep	Outcome measures and Scores	Results	Conclusion
Desando *et al.*, 2017: The regenerative potential of autologous matrix-induced BMAC and autologous chondrocyte implantation. (ACI) in talar OCL	-PCS -Level: II -total n = 22 (mACI, n = 7; mBMAC, n = 15)	Surgery: Arthroscopic implantation of mBMAC or mACI for talar OCL repair -Follow-up: up to 36 mos	mACI: cultured cells onto periosteal flap or grown on HYAFF-11. mBMAC: cell separator-concentrator Cells: 1 x 10^6 seeded on 1x1 cm 2mm thick scaffold	-Assessment AOFAS (12, 24, 36 mo) - cartilage histology after 24 mo	-AOFAS improved in both groups, but mACI showed the best response -mBMAC group had a higher expression of fibrous and hypertrophic markers (e.g. Collagen X)	mACI treatments seem superior over mBMAC treatments in talar OCL
Vannini *et al.*, 2017: - BM-derived cell transplantation in talar OCL	-Comparative study -Level: II -n = 140	Surgery: -Arthroscopic BM-derived cell transplantation - Follow-up: 48 mos	BMAC: cell separator. 3 different scaffolds (for availability reasons): collagen powder, HYAFF-11, collagen membrane	-AOFAS -Halasi	AOFAS improved at 24 and 48 mo) -Halasi score improved from 6.88 to 5.56 at 48 mos	BM-derived cell transplantion in the repair of talar OCL showed clinical improvement
Karnovsky *et al.*, 2018: Comparison of the functional and radiological outcome of JACI-BMAC *vs* MF surgery for talar OCL repair	-comparative series, retrospective chart review - Level: III -n = 50 (microfracture, n = 30 of which 17 received supplemental BMAC; JACI-BMAC, n = 20)	Surgery: JACI-BMAC implantation *vs* MF - Follow-up: 12-79 mos (mean 30.9 mos)	JACI-BMAC: aspiration and concentration (Magellan)	-VAS -AOFAS -MOCART	Both groups showed improvement in FAOS and VAS, but VAS improvement was only significant in MF -OCL diameter was larger in JACI-BMAC, with more hypertrophy on MRI	JACI-BMAC and MF both improve clinical outcome. -JACI-BMAC treatment revealed no significant functional gains compared to MF

Study	Model	Treatment	ASC prep	Outcome measures and Scores	Results	Conclusion	
D'Ambrosi *et al*., 2018. Arthroscopic management of in talar OCL with MFAT	-case series -Level: IV -n = 4	Surgery: Microfracture and MFAT - Follow-up: 6 mos	MFAT/ADSCs (LipogemsSystem protocol)	-AOFAS -VAS -SF12	All four patients reported clinical improvement without complications	Arthroscopic treatment of talar OCL with MFAT resulted in clinical improvement and provided reliable pain relief
Murphy *et al*., 2019: Outcomes of MF with and without BMAC in ankle OCL repair	-PCS (cohort) -Level: III -n = 101 (MF, n = 52; MF/BMAC, n = 49	Surgery: MF with or without BMAC -Follow-up: MF group minimum of 54 mos (mean 58 mos), MF/BMAC group minimum 30 mos, (mean 40 mos)	BMAC concentrator (Harvest system).	-Self-reported patient outcome -VAS -Pre and postop symptom, pain, sport, QOL and ADL score -Revision rate	Both groups revealed improvements in pain, QOL, ADL scores. -revision rate was higher in MF only group	MF with BMAC is well tolerated and decreases revision rates in talar OCL repair
Penner *et al*., 2020, Pilot study: Arthroscopic repair talar OCL with Umbilical cord allograft	-PCtS -Level: II -n = 10	Surgery: -Arthroscopic treatment with umbilical cord allograft -Follow-up: 6, 12, 24, 52 wks	Umbilical cord: CLARIX CORD 1K, Amniox Medical, Miami, FL	-AOS -FAAM -VAS (6, 12, 24, 52 weeks) -SF-36 -CT/MRI	-Improvement in all outcome measures -Pain scores improved significant -reduced OCL size	Athroscopic repair and adjunct umbilical cord allograft is a promising treatment option for talar OCL

However, various methodological concerns about this study have been brought up, including the lack of a detailed description of the PRP preparation and characterization, the differences in baseline characteristics between the two groups (specifically the higher BMI and greater proportion of patients with more advanced stage OA in the PRP group), and the appropriateness of the outcome measure that was used (128).

Adult stem cells for the treatment of ankle osteoarthritis

Four publications met our inclusion criteria: three case series (level II, III, and IV studies) (129-131), and one retrospective comparative study (level III) (131). Two investigated the clinical benefit of injections without surgery (129, 130), and two studies focused on the combination of surgery and ASC injections (131, 132).

Both whole bone marrow injections alongside hyperosmotic dextrose and BM-derived MSC injections were used for ankle OA and showed improved pain scores and ankle function (129,130). Kim and colleagues revealed that arthroscopic marrow stimulation (calcaneal osteotomy or supramalleolar osteotomy) combined with adipose-derived MSC treatment had a significantly positive effect on clinical outcomes compared to marrow stimulation alone (131, 132). Interestingly, the degree of talar tilt angle correction was correlated with the clinical outcomes, and the ICRS grade was considerably enhanced in patients who received an MSC injection in addition to marrow stimulation and osteotomy. These studies indicate that BM-MSC injections as an adjunct to arthroscopy and osteotomy are generally safe for the treatment of ankle OA and may provide significant benefits in cartilage repair.

DISCUSSION

The use of viscosupplementation and orthobiologics for the treatment of joint disease is an area of ongoing research. Regenerating cartilage is possible with the use of different orthobiologics and evidence is accumulating that patients who receive orthobiologic treatment for joint disease experience improvement in pain and function. Several groups have assessed the efficacy and safety of HA, PRP and ASCs in ankle OCL and OA treatment, with varying approaches.

Hyaluronic acid in osteochondral lesions of the ankle

The low rate of adverse effects seen after HA injections has been demonstrated by all HA injection studies included in this review (**table III**). The beneficial effects of HA injections were evident in the first 12 weeks, which would likely be explained by the anti-inflammatory effect (86). Patients who experienced continued pain after arthroscopic procedures reported pain relief after HA injections, implying that HA can be considered as a nonsurgical alternative among these patients. Long-term, early administration of HA injections following arthroscopic MF in talar OCL enhanced the improvement in pain and function scores (87, 88). It is important to note that high-molecular weight, cross-linked HA generally results in better outcomes than low-molecular-weight, non-cross-linked HA (115, 122). MF surgery by itself improved ankle pain and function, but MF with a post-operative HA injection improved clinical outcomes even further, revealing additional effects of HA. Although the reports on HA treatments are promising, high-level studies are required to provide more substantial evidence for this treatment option.

Platelet-rich plasma in osteochondral lesions of the ankle

PRP appeared to promote functional recovery and pain relief in talar OCL to a greater degree than HA (91, 93). PRP contains a mixture of bioactive cytokines such as TGF-β1, insulin-like growth factor (IGF-1), and inhibitors of metalloproteinases, which play a role in joint repair and cartilage protection (133, 134). In addition, PRP enhances synovial fluid quality by the induction of synovial HA secretions (135). All these factors combined can explain the superior results of intra-articular PRP injections compared to HA.

Similar to HA, the use of PRP in the treatment of talar OCL revealed minimal adverse effects (**table IV**). Previous intra-articular PRP injection studies show a median benefit duration of 9 months, and a reduction in the beneficial effects after 12 months (91, 92, 136). Future studies should include at least a 24-month follow-up period to further determine its lasting effects.

The follow-up period of adjunct injections after surgery varies from 12 months to 84 months (**table IV**), which provides valuable information on the medium and long-term effects of adjunct PRP injections. Overall, maximal beneficial effects were observed between 5- and 13-weeks post-injection.

PRP injection for the treatment of talar OCL is a viable option, and its benefit as an adjunct therapy after surgery is maintained and preferred over surgery alone. PRP appears superior to HA and is recommended as the primary adjunct treatment option in talar OCL. With surgery, mosaicplasty and PRP revealed better outcomes compared to MF and PRP. Future studies may focus on long-term follow-up periods and multicenter trials.

Adult stem cells in osteochondral lesions of the ankle

Randomized clinical trials and studies focusing on nonsurgical treatments for talar OCL are currently lacking (**table V**). The first study describing an arthroscopic ACI for OCL was reported by Giannini and colleagues (2009) and revealed improved function and cartilage regeneration (99). Their results were confirmed by others (97, 98). JACI-BMAC combined with MF revealed no significant functional gains compared to MF alone and resulted in fibrocartilage tissue rather than normal cartilage tissue (102). Understanding the characteristics of the specific BMAC used in future studies with additional outcome measurements like histology could elucidate the beneficial effects of JACI-BMAC.

Arthroscopic implantation of matrix-induced BMAC on periosteal or HA scaffolds seemed inferior to matrix-induced ACI and also showed increased expression of fibrosis markers and the hypertrophic marker Collagen X (103). Other factors that decrease therapeutic success include patient age and previous cartilage repair surgery, and data should be corrected for these factors (99). MFAT seems especially beneficial in patients older than 50 years of age, and when lesion size exceeds 109 mm^2, which is an important finding and should be explored further (106).

As BMAC and collagen matrices were shown to enhance bone integration (74, 104), and initial results revealed PJAC to be preferred over BMAC scaffolds (105), future studies focusing on these options with more patients will provide useful information. Bone marrow stimulation combined with injections showed better results than bone marrow stimulation without injections or scaffolds. Even though ACI resulted in superior AOFAS scores, future studies should focus on high-quality trials and high level of evidence studies with longer follow-up periods comparing ASCs alone with ASCs combined with surgery and with surgery alone. Other factors that need elucidation include the correlation between outcomes and lesion number, size, and location, joint and cartilage remodeling, histology, the presence of subchondral cysts, and imaging studies. Overall, current data are in favor of ASCs in talar OCL repair and regeneration.

Hyaluronic acid in ankle osteoarthritis

HA for ankle OA has received considerable investigative attention compared to PRPs and ASCs. The high number of level I and II studies has increased its use in clinical practice over the years. Out of all the HA ankle OA studies, only one report combined surgery with injections (**table VI**).

Patients have reported improvements in pain and function scores in as little as 6 months (115, 119) and in AOS scores up to 18 months (114). However, some patients occasionally required an additional HA injection after the initial injection for persistent pain (86, 115). Given the observation that three weekly 1 ml HA injections were more effective in reducing pain (21, 120) than single 1 ml, 2 ml, or 3 ml injections (120), studies focused on multiple injections in high-quality trials are recommended. Current guidelines note that HA is safe for use in the ankle joint and can be considered in patients who do not respond to first-line interventions, though it is still unclear as to which subset of patients respond most favorably to HA (137).

Platelet-rich plasma in ankle osteoarthritis

Three PRP studies for ankle OA included in this paper were evidence level III or IV, while one study was evidence level I (**table VII**). All studies reported the use of nonsurgical PRP injections. The three level III/IV studies demonstrated improved pain scores using PRP injections in ankle OA, with early-stage OA responding better to PRP injections than late-stage OA. This could be partially explained by the fact that the early-stage OA joint has enough synovium, less metalloproteinases, cytokines and TNF, and only mild soft tissue destruction, allowing PRP to induce proliferation and expansion of chondrocytes (62). These processes are likely hampered in late-stage OA.

Four weekly PRP injections improved pain scores in patients who did not benefit from HA or arthroscopic surgery (126). Since the composition of PRP can vary, more data regarding the optimal concentration, frequency and number of injections will be crucial for the future use of PRP in ankle OA.

The one double-blinded randomized clinical trial comparing two intraarticular PRP injections to placebo injections found no difference in mean pain and function scores after 26 weeks, though noted no significant adverse events related to the injections (127). However, the PRP group had a higher body mass index and higher proportion of patients with more advanced stages of OA and there is concern that these between-group differences in baseline characteristics may have led to confounding bias (128). Furthermore, since the authors did not provide a detailed description of the PRP preparation and characterization, it is unclear whether the patients in the intervention group received a dose of platelets that would lead to clinical improvements (128).

Overall, it seems that PRP injections in ankle OA are a safe option that can be considered for patients unfit for invasive surgical procedures and for the treatment of younger patients.

Adult stem cells in ankle osteoarthritis

The use of ASCs has been studied more frequently in knee OA and talar OCLs than in ankle OA. In addition, studies comparing the role of adipose-derived tissue or cell therapy in ankle OA are still scarce (**table VIII**). The clinical benefit

Table VI. HA and osteoarthritis of the ankle.

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Salk *et al.*, 2006, Pilot study: Efficacy and safety of intra-articular HA injections for ankle OA	-RCT-DB -Level: I -n = 20 -control: saline -5 HA injections, one/week	Injection: Intra-articular injection of HA or saline - Follow-up: 6 mos	-AOS -WOMAC -sGFS -Pain score (5 points) -Ankle Girth -Ankle ROM -EQ-5D -SF-12	-Improved mean AOS in both groups -5/9 in HA group >30mm improved AOS, *vs* 1/8 in saline group	5 weekly intra-articular HA injection was well-tolerated, provided pain relief, and improved function in ankle OA
Sun *et al.*, 2006: Efficacy, safety, and duration of therapy intra-articular HA injection in ankle OA	-PCS -Level: II -n = 93 (75 completed the study)	Injection: 5 intra-articular HA injections, one/week, compared to baseline (no control injection) -Follow-up: up to 6 mos after 5th injection	-AOS -AOFAS -ROM -sGFS -Local AEs	-Significantly improved AOS and AOFAS -sagittal ankle ROM was poorly improved -Local AEs in 6.7% -pain medication consumption decreased	5 weekly injections HA provided pain relief, functional improvements in ankle OA -effect was seen after 1 wk, lasting > 6 mos
Carpenter & Motley 2008: Pain reduction following ankle arthroscopy with or without 3 weekly intra-articular HA injections	-PC -Level: IV -N = 26	Injection and surgery: Arthroscopy with and without 3 weekly intra-articular HA injection -Mean follow-up: 13-14 mos	-10 point categorical pain score at 3 mos	- Significant decrease in pain in both groups -Better response when HA injections were given after arthroscopy	HA injections adjunct to arthroscopy are more beneficial than arthroscopy alone in the treatment ankle OA
Cohen *et al.* 2008: Safety and efficacy of intra-articular HA *vs* PBS in ankle OA	-RCT-DB -Level: I -n = 28 (of which 15 HA and 13 saline control)	Injection: Intra-articular injection of HA or saline -Follow-up: 6 mos	-AOS -WOMAC -Global assessment -SF12	-Improvement: HA > control -Few adverse events -no post-infection flare	HA is safe and effective for pain associated with ankle OA -Larger studies needed
Karatosun *et al.*, 2008: Intra-articular HA injection *vs* exercise in ankle OA	-RCT (Prospective) -Level: I -n = 30 pt (43 ankles)	Injection: Intra-articular injection of HA -Follow-up: 12 mos	-AOFAS	-AOFAS improved in both groups (61.6 to 90.1 with HA, 72.2 to 87.5 with exercise) -no statistically significant differences	-Both HA and exercise provide equal functional improvement. -Larger trials and longer follow-up needed

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Luciani *et al.* 2008: Evaluation of intra-articular HA injections HA in ankle OA, three weekly injection	-PCS -Level: II -n = 21	Injection: Intra-articular injection of HA, 3 weekly -Follow-up: 18 mos	-AOS	Significant improvement of AOS up to 18 mos	AOS was improved when given HA injections for ankle OA, lasting at least 18 mos
Witteveen *et al.* 2008: Intra-articular HA injections in ankle OA	-PCS -Level: II -n = 55	Injection: Intra-articular injection of HA -Follow-up: 3 mos	-VAS	-No serious adverse events -n = 17 had mild/ moderate AEs -VAS decreased from 68 to 33.8, maintained up to 6 mo -24 patients received a 2nd HA injection for persistent pain	HA injections for ankle OA are well-tolerated and effective up to 6 mos
Mei-Dan *et al.*, 2010: Evaluation of the efficacy of intra-articular HA injections for ankle OA	-PCS -Level: II -n = 16 (15 completed study)	Injection: Intra-articular injection of HA -Follow-up: 32 wks	-VAS -AOFAS	-Improvement in 13 of 15 patients: significant VAS and AOFAS improvement	-Intra-articular HA injections in ankle OA resulted in significant improvements lasting for >7mos
Witteveen *et al.*, 2010: Efficacy, safety and dose dependency of intra-articular HA injections for ankle OA	-PRCT -Level: II -n = 26 -4 groups: 1 ml, 2 ml or 3 ml injection group and 3 weekly 1 ml injection group	Injection: Intra-articular injection of HA -Follow-up: 27 wks	-VAS (at night, when walking, at rest)	-3x1 group: significant decrease in pain at wk 7 (walk and rest) At wk 15: significant decrease in pain at rest	HA injection in ankle is effective and well-tolerated. -3 x 1 ml injections showed best results
Sun *et al.* 2011: Evaluation of safety of three weekly injection of HA in ankle OA	-PCS -Level: II -n = 50 pt (46 completed the study)	Injection: Intra-articular injection of HA -Follow-up: up to 6 mos	-AOS -AOFAS -balance test -use of analgesics -sGFS	-Significant reduction of AOS at 1, 3, 6 mos after the third injection. -AOFAS improved from 60.5 to 73.5, 75.5 and 76.7 at 1, 3, 6 mos. -Improved balance -decreased analgesic use	-Three weekly injections of HA are well tolerated, provide pain relief, and improve ankle function in ankle OA -Larger studies needed

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
DeGroot *et al* 2012: Effectiveness of a single intra-articular injection of HA *vs* saline for ankle OA	-RCT-DB, placebo controlled -Level: I -n = 64 (56 completed the study)	Injection: Intra-articular injection of HA or saline -Follow-up: 12 wks	-AOFAS -AOS -VAS	-1.6% experienced AEs -AOFAS for AH improved by 4.9 points - AOFAS for saline decreased by 0.4 points (wk 6), and improved by 5.4 points (wk 12)	Intra-articular HA injections are not superior to saline injections for treatment of ankle OA
Lucas y Hernandez *et al.* 2013: Evaluation of efficacy intra-articular HA injections in ankle OA	-PCS -Level: II -n = 18 pts (26 ankles)	Injection: Intra-articular injection of HA, three injections (= 1 series) with each injection 15 days apart, new series if effect reduced after 1 year, up to 3 series in total. - Follow-up: 22.5-71.8 (mean 45 mos)	-AOFAS -patient satisfaction	-11 patients received 1 series, 6 patients 2 series and 1 patient 3 series. -AOFAS increased from 61.8 to 74.4 (4 mo) and 73.7 (12 mo). -no AE	HA injections for ankle OA was most effective when three injection protocol with fluoroscopy was used, every 2 years
Mei-Dan *et al.*, 2013: Intra-articular injection of HA for subtalar joint OA	-longitudinal study -Level: IV -n = 22	Injection: Intra-articular injection of HA (Euflexxa) - Follow-up: up to 28 wks	-AOFAS -VAS -Maximum walking distance -Pain frequency -Selective global function	-Improved AOFAS and VAS -global assessment improved in 18 pts -walking distance improved, lasting for > 6 mos	Intra-articular injection of HA should be considered in conservative management of subtalar OA
Witteveen *et al.*, 2013: Comparison of 2 HA injection techniques in OA ankle	-RCT (crossover) -Level: I -n = 70	Injection: Intra-articular injection of HA (2 techniques: with and without traction devise) -Follow-up: 3 mos	Failure rate of the injection	-failure rate for both techniques was 24%. -41 patients in traction and 39 in non-traction group experienced local AEs	-No significant difference in the 2 techniques -Fluoroscopy for injection in severe OA is advised

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Han *et al.*, 2014: Identification of baseline prognostic outcome factors after HA injections in ankle OA	-RCS pt tx w/ HA inj -Level: 3 -n = 40, mean age 60.6	Injection: Intra-articular injection of HA -Follow-up: up to 12 mos	-VAS -predictors: gender, age, symptom duration, radiograph OA stage, subchondral cysts, fracture history -patient satisfaction	-Mean VAS 3,6,12 mos: 3.6, 4,3, 5,3 resp. -Early stage disease was independent predictor associated with positive VAS outcome -early stage disease and duration less than 1 year were independent predictors associated with higher satisfaction	-HA injections are effective but selection of the patient should be made accordingly for successful treatment
Sun *et al.*, 2014: Compare efficacy intra-articular BoTox or HA injection plus rehabilitation exercise in ankle OA	-PRCT -Level: I -n = 37 (HA), n = 38 (BoTox)	Injection: Intra-articular injection of HA plus exercise or BoTox -Follow-up: 6 mos	-AOS -AOFAS -VAS -SLS -TUG -Need for analgesics -sGFS	-No significant between-group differences in total AOS score, pain subscale, disability score -No significant difference in AOFAS, VAS, SLS, TUG scores or analgesic use. -HA group improved more in SLS than BoTox group	-BoTox or HA plus exercises were equally effective, improved function and balance in ankle OA patients -Rapid effect at wk 2, may last for at least 6 mos
Bossert *et al.*, 2016: Intra-articular injection of HA in ankle OA; image guided or landmark guided?	-RCS -Level: III -nonanimal crosslinked HA and Mannitol -n = 50	Injection: Intra-articular injection of HA -Follow-up: 12 mos	-Self-evaluation of pain -satisfaction -tolerability -efficacy	-(Very) satisfied and not really/dissatisfied: 68 and 32% -efficacy highly correlated with pain score -success rate image guided 2.3x higher than landmark -tolerability very good/good in 47 patients	Use of image guided injection optimizes success rate ankle viscosupplementation -no safety concern
Murphy *et al.*, 2017: Intra-articular injection of HA in ankle OA	-PCS -Level: II -n = 50, 3-inj protocol sodium HA ankle	Injection: Intra-articular injection of HA -Follow-up up to 16 mos (mean 12 mos)	-AOFAS	AOFAS pretreatment 48 and posttreatment 78	Intra-articular injection of sodium HA is a useful conservative treatment option for ankle OA
Younger *et al.*, 2019: Nonanimal intra-articular HA injection for ankle OA	-Prospective single-arm cohort study - Level: IV -n = 37	Injection: Intra-articular injection of HA -Follow-up: 26 wks	-VAS	- VAS reduction 34% -5 patients had AEs	NASHA in treatment of ankle OA (single injection) reduced pain and disability during 26-week period

Table VII. PRP in osteoarthritis of the ankle.

Study	Model	Treatment	Outcome measures and Scores	Results	Conclusion
Angthong *et al.*, 2013: Determination of QoL outcomes after PRP treatment in hindfoot and ankle diseases	-RCS -Level: III -n = 12 (of which 5 patients with ankle OA) -PRP prep: Arthrex (leukocyte poor)	Injection: -PRP in perilesional area under fluoroscopic or ultrasound guidance -Follow-up: up to 22 mos (mean 16 mos)	-VAS-FA pre- and post-injection - SF-36 score	-VAS pretreatment: 57.89 -VAS final FU: 79.71 -unsatisfactory results: n = 4 (33%) -SF-36: satisfactory group: 85.23 - SF-36: unsatisfactory group: 57.33	Potential benefit of PRP injections, but unsatisfactory results have been reported, warranting further studies
Repetto *et al.*, 2016: Evaluation of mid- to longterm results of PRP injections for ankle OA	-RCS -Level: III - n = 20 -PRP prep: Hettich Centrifugations (leukocyte poor)	Injection: -intra-articular PRP (4 weekly LP-PRP) -Follow-up: 12-30 mos (mean 17.7 mos)	-FADI -VAS	pre- *vs* post-treatment scores: -FADI: 59.22 *vs* 80.21 -VAS: 7.8 *vs* 2.6 -10% required surgery because of early treatment failure	PRP injections for ankle OA are safe and can be opted for to postpone ankle surgery
Fukawa *et al.*, 2017: Assess safety and efficacy of intra-articular PRP injections in ankle OA	-PCS -Level: 4 -n = 20 -PRP prep: Blood Separation Pack Kawasumi (activated PRP)	Injection: -3 US guided intra-articular PRP injections, 2 wk interval -Follow-up: 24 wks	-VAS -JSSF -SAFE-Q	-VAS and JSSF significantly decreased -SAFE-Q improved significantly at wk 12 - VAS lowest at 12 wks - Scores for late stage OA worse than early stage OA	Intra-articular injection of PRP for ankle OA significantly improved pain and function scores
Paget *et al.*, 2021: Effect of PRP Injections *vs* Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial	-RCT-DB -Level: 1 -n = 100 -PRP prep: Arthrex double syringe PRP system (leukocyte poor)	Injection: 2 US guided intra-articular PRP injections, 6 wk interval -Follow-up: 26 wks	-AOFAS	-AOFAS improved by 10 points in PRP group and 11 points in placebo group; the difference was not statistically significant between groups	Intra-articular injections of PRP for ankle OA did not improve pain and function compared to placebo

of nonsurgical BMAC treatments revealed improved pain scores and ankle function in a small study (129) and in a larger study with a follow-up period of up to 30 months (130). Post-injection MRIs showed repair and thickening of joint cartilage. In future studies, we need to determine the correlation between the number of ASCs per injection and the clinical outcome. As improvements declined after 12 months, it would also be interesting to test whether repeat injections provide additional or longer benefits.

Kim and Koh (2016) demonstrated the beneficial effect of the adjunctive use of adipose-derived MSCs compared to surgery alone (131). These MSCs seemed to enhance cartilage regeneration determined by second-look arthroscopy, but unfortunately there was no histological comparison. Comparing histological data pre- and post-ASC treatment can provide useful data on the regenerative potential and quality of cartilage. Therefore, future studies should include tissue analysis and radiographic evidence with increased sample sizes in a randomized prospective setting. BM-MSC injection alone seems to be a safe alternative treatment option to improve function and potentially regenerate cartilage in ankle OA patients. The improved ICRS grade found when ASCs are combined with surgery is a promising result and should be explored further.

Table VIII. ASCs in osteoarthritis of the ankle.

Study	Model	Treatment	ASC prep	Outcome measures and Scores	Results	Conclusion
Hauser & Orlofsky 2013: Injection of whole bone marrow in hip, knee, ankle in combination with hyperosmotic dextrose	-CS -Level: 4 -n = 7 -2-7 treatments over 2-12 mos	Injection: MSC injection (unfractionated whole bone marrow and hyperosmotic dextrose) -Follow-up: 2-12 mos (mean 7 mos)	-Tibial and/ or iliac bone marrow aspiration	Patient reported assessments	Improved pain, function, and QoL. -3 patients experienced (near-)complete symptom relief	Whole bone marrow injections for ankle OA improved both pain and function scores, but given the low patient case count, additional studies are needed
Emadedin *et al.*, 2015: Safety of autologous BM-derived MSCs tranplantation in OA (knee, ankle or hip)	-PCS -Level:2 -n = 18 (but 17 analyzed)	Injection: Iliac BM-derived MSC. -Follow-up: evaluation pre-injection, 2, 6, 12, and 30 mos	BM-MSC: aspirate in PBS and EDTA, centrifugation, cultured 7d. Before injection: Isolation and Trypsin/ EDTA treatment	-Clinical exam -MRI -Lab test -VAS -WOMAC	-no severe AEs -Improved walking -decr VAS and WOMAC	MSC injection in OA is safe and therapeutically beneficial -larger sample size needed
Kim & Koh, 2016: Comparing the outcome of arthroscopic marrow stimulation combined with calcaneal osteotomy in ankle OA, with or without adipose-derived MSC injection	-RCS -Level:3 -n = 49, (23 marrow stimulation, 26 marrow stimulation with MSC injection)	Surgery and injection: Second-look arthroscopy after arthroscopic marrow stimulation, combined with lateral sliding calcaneal osteotomy -Follow-up: 24-34 mos (mean 27.6 mos)	Liposuction and centrifugation	-VAS -AOFAS -ICRS grade -radiologic outcome variable was talar tilt angle	Mean VAS and AOFAS improved, especially in marrow stimulation/ MSC group. -ICRS correlated with clinical outcomes. -Talar tilt angle improved after lateral sliding calcaneal osteotomy in both groups	Varus ankle osteoarthritis treatment with lateral sliding calcaneal osteotomy showed a better outcome with BMS and MSC injection compared to without
Kim *et al.*, 2016: Compare clinical, radiological, and second-look arthroscopic outcomes between marrow stimulation with or without MSC injection in ankle OA after supramalleolar osteotomy	-RCSt -Level:3 -n = 62 patients (64 ankles, of which 33 treated with marrow stimulation, and 31 with marrow stimulation and MSCs)	Surgery and injection: Arthroscopic marrow stimulation with or without MSC injection in ankle OA following supramalleolar osteotomy -Follow-up: mean 12.8 mo	MSC: liposuction and centrifugation	-VAS -AOFAS -Radiology -TAS -TT angle -TLS -ICRS grade	-VAS and AOFAS improved -ICRS correlated with clinical outcome -TAS, TT and TLS angles improved significantly after SMO in both groups, not significantly correlated with outcomes or ICRS	Clinical and second-look outcomes of MSC injection with marrow stimulation were better compared to without MSC in varus AO following supramalleolar osteotomy

CONCLUSIONS

We have outlined the current literature describing the clinical use and outcome of HA, PRP, and ASC therapies in ankle OCL and OA. HA was shown to be a safe treatment option with a low rate of adverse effects and overall clinical improvement. The use of PRP injections for the treatment of joint disease is also a viable option and seemingly equal to PrT, although confirmation of this latter result is warranted. Importantly, PRP is the superior and recommended adjunct treatment option over HA in talar OCL patients. The combination of surgery and PRP injections revealed improved clinical outcomes *versus* surgery alone. Alternatively, patients unfit for invasive surgical procedures may benefit from PRP injections without surgery. Of note, a high-level RCT is lacking for ASC studies in talar OCL and ankle OA, and should be a focus in the coming years. Comparative histological and molecular analyses of newly formed cartilage should be considered in future studies to fully address the regenerative potential of orthobiologics.

Overall, our review demonstrates that HA and orthobiologics can be used as a pre-surgical treatment in ankle OCL and OA or as a second-line treatment for patients who remain symptomatic after surgery. The safety profile and subjective improvement in clinical outcomes following orthobiologic treatments seem promising. As the number of studies is growing, more data will be available to allow standardized therapies and timed interventions.

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DATA AVAILABILITY

All data used in this review is appropriately cited.

CONTRIBUTIONS

EYR, MSR, KCM, HB, JBS: formulation of study idea. EYR, MSR, KCM, DRB, HB, JBS: literature review and article selection, manuscript writing.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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