Current Concepts in Osteoarthritis of the Ankle: Review

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ABSTRACT

Ankle osteoarthritis constitutes a large burden to society and is a leading cause of chronic disability in the United States. Most commonly, it is post-traumatic, occurs in younger individuals, and is associated with obesity. This entity presents similarly to osteoarthritis of the other joints, with the typical nonspecific symptoms of stiffness, swelling, and pain. Radiographic investigation includes four weight-bearing standard views: antero-posterior and lateral foot, mortise view of the ankle, and a specialized view of the hindfoot. In this review, we covered epidemiology, anatomy and biomechanics, etiology, pathology, differential diagnoses, symptoms, physical examination, appropriate radiological investigation, as well as current treatment options and algorithms. Non-operative treatment options include weight loss, physical therapy, bracing, orthoses, pharmacologic treatments, corticosteroid injections, viscosupplementation, and biologic

modalities. Viscosupplementation with hyaluronic acid has the most evidence-based support and has been shown to be safe and efficacious. For patients who have moderate to severe disease, surgery may be indicated. However, current surgical options are either associated with high rates of complications or restrict ankle range of motion (ROM). Early stages of the ankle osteoarthritis should be treated with the above-mentioned non-surgical methods, and once the disease progresses, surgical options can be utilized.

INTRODUCTION

Although ankle osteoarthritis (OA) occurs in only 1% of the world's population, it is a leading cause of chronic disability in the United States and Canada.[1] In a cross-sectional study of 130 patients who had end-stage ankle arthritis, the physical disability was shown to be two standard deviations higher than that of the general population (30 vs. 52; $p<0.05$), which is similar to end-stage osteoarthritis of the hip joint, end-stage kidney disease, or heart failure.[1] Agel et al. administered a Musculoskeletal Functional Assessment (MFA) survey to 426 patients who had ankle arthritis and 123 patients who did not, and they demonstrated significantly worse mean MFA scores in ankle arthritis patients (40 vs. 9 points; $p<0.05$).[2]

Primary ankle osteoarthritis usually afflicts an older population (mean age, 65 years), but it is not as common as post-traumatic osteoarthritis, which can present in patients in their early 20s (mean age, 58 years).[3] In a statewide Iowa database, the symptomatic ankle osteoarthritis was estimated to have an incidence of 1,516 and a prevalence of 22,125 cases.[4] Using 2015 United States Census Bureau Iowa State data (3,123,899 individuals) and the United States (321,773,631 individuals) data, we can extrapolate the national incidence to approximately 156,000 and the prevalence of approximately 2,279,000 cases. The lifetime cost of treating a single patient who has ankle arthritis is approximately $50,000,[5] and utilizing an average life expectancy of 79 years, the annual cost of ankle osteoarthritis treatment in the United States is approximately $1.5 billion.

Various non-operative and surgical treatment methods have been investigated and developed for the treatment of this disease.[6] Similar to osteoarthritis of other joints, early disease is treated non-operatively with physical therapy, pharmacotherapy, injections, and orthoses. In more severe cases, operative treatment can be utilized. However, due to the younger mean age in this population of patients, and their long life expectancy, a non-operative treatment is desired. Therefore, the aim of this review is to provide an up-to-date, evidence-based guide for the diagnosis and treatment of ankle osteoarthritis. We discuss the epidemiology, anatomy, biomechanics, etiology, as well as the pathology of ankle osteoarthritis, and update the readership on recent advances in diagnosis and treatment of this disease.

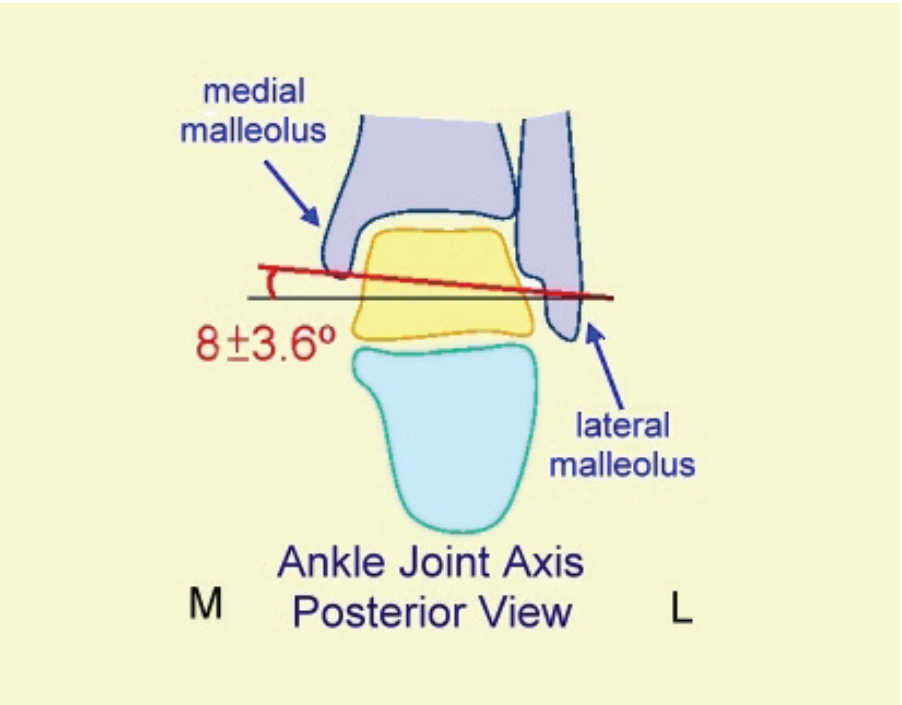

Figure 1. Ankle joint axis of rotation (by Vinit Kothekar, labeled for reuse).

1.EPIDEMIOLOGY OF ANKLE ARTHRITIS

Primary idiopathic osteoarthritis of the ankle is a rare phenomenon (approximately 9% of total arthritis incidence) with secondary (13%) and post-traumatic osteoarthritis being more common (78%).[7,3] According to one study, approximately 6 to 13% of all osteoarthritis involves the ankle.[1] Some patient populations have a higher risk of developing this condition. In a study of 1,411 adults, Frey et al. demonstrated that overweight and obese individuals (body mass index [BMI] $\geq$ 25 kg/m^2) have a 1.5 times increased likelihood of developing ankle osteoarthritis ($p<0.05$, 95% CI 0.986 to 2.274).[8] In a comparative study of female ballet dancers and the general population (27 vs. 38 subjects respectively), van Dijk et al. demonstrated that the female ballet dancers had a higher risk of developing ankle arthritis (11 of 27 vs. 0 of 38; $p<0.043$).[9]

In a cadaver study, Muehleman et al. demonstrated that of the 1,060 extremity pairs, knee arthritis was much more common than in the ankle; however,

they did not observe any cases of ankle arthritis that were not associated with ipsilateral knee disease.[10] Interestingly, they noted that the earliest signs of ankle degeneration were in a 28-year-old patient. In addition, only 1 to 3% of ankles had more severe OA of the ankle than the knee. There was no difference in the severity of disease between obese and non-obese subjects ($p>0.05$).[10] However, this is a cadaver study, and several other studies have demonstrated that obesity is a risk factor for the development of ankle OA.[8,11,12]

2. ANATOMY AND BIOMECHANICS

The ankle, also known as the talocrural joint, is a synovial hinge-type joint composed of the tibia, fibula, and talus, which allows for dorsiflexion and plantarflexion movements in the sagittal plane.[13] The medial side of the joint is formed by the medial malleolus of the tibia, and the lateral side of the joint is formed by the lateral malleolus of the fibula. The axis of rotation is oblique to both sagittal and frontal planes (approximately 8 to 10° from the transverse plane) (Fig. 1).[14] Normal range of motion (ROM) is 0 to 30° for dorsiflexion and 0 to 55° for plantarflexion.[14] The articular surfaces are located on the distal inferior aspect of the tibia (plafond) and fibula proximally, and the talar dome distally.[13] The articular surface area is smaller when compared to the hip and knee joint, but the cartilage resistance is higher.[13] Shepherd and Seedhom measured the thickness of 11 stets of cadaver joints and demonstrated that the cartilage in the ankle joint was thinner (1.0 to 1.2mm vs. 1.69 to 2.0mm; $pp<0.001$), more uniform, and had a higher compressive modulus when compared to the knee joint.[15]

Normally, the ankle joint has approximately 3mm width between the tibia and talus, a medial space of approximately 3 to 4mm, and a lateral space of 5mm.[16] In osteoarthritis, cartilage deterioration and loss secondary to trauma, poor biomechanics, infection, or inflammatory changes results in the narrowing of these spaces and denudation of the subchondral bone surfaces.[8] This may lead to altered gait patterns in these patients.[17] In a study of 15 patients with and 15 patients without ankle arthritis, Valberrabano et al. demonstrated reduced total plantar flexion movement (-37.5%), total inversion movement (-28.4%), total adduction movement (-19.8%), as well as maximal plantar flexion movement (-13.8%), and maximal adduction movement (-44.4%) in ankle arthritis patients when compared to the normal subjects.[18] In addition, cadence (-9.1%), walking speed (-16.2%), stride time (+9.4%), step time (+13.2%), stride length (-6.7%), and step length (+7.2%) were different from normal subjects.[17]

3. ETIOLOGY OF ANKLE OSTEOARTHRITIS

A history of ankle trauma or recurrent instability which results in irreversible cartilage damage are the most common etiologies of ankle osteoarthritis.[6] In a study of 639 patients that presented with Kellgren-Lawrence grade 3 or 4 ankle arthritis at a large academic center, Saltzman et al. identified the etiology of the disease based on the medical history, physical examination, and imaging.[19] Of these patients, 445 (70%) were identified to be post-traumatic, 76 (12%) due to rheumatoid disease, and 46 (7%) were idiopathic (primary) osteoarthritis. Most of the patients that were diagnosed with post-traumatic ankle arthritis had a prior rotational ankle fracture in the past. Half of the patients diagnosed with primary osteoarthritis had malalignment of the hindfoot, which could have been the predisposing reason for the development of the degenerative joint disease.[19]

In a similar study, Valderrabano et al.[3] identified 390 patients (406 ankles) who presented to a single institution and classified them into post-traumatic arthritis (n=318, 78%), secondary arthritis (n=52; 13%), and primary osteoarthritis (n=36; 9%). The most common traumatic injuries were identified to be fractures of the malleoli (157), tibial plafond (58), talus (9), tibial shaft fractures (20), and ankle ligamentous injuries (65). Secondary osteoarthritis cases included rheumatoid arthritis (22), hemochromatosis (11), hemophilia (6), clubfoot (4), osteonecrosis of the talus (3), osteochondrosis dissecans (3), and post-infectious arthritis (3). Patients who had primary osteoarthritis were significantly older than the post-traumatic and secondary cohorts (65 vs. 58 and 57 years; $p<0.05$). Those who had secondary osteoarthritis, had significantly higher pain scores than post-traumatic and primary cohorts (7.0 vs. 6.9 and 6.1 points). The primary osteoarthritis cohort had the highest range of motion (28°) when compared to the other two cohorts (22 for post-traumatic and 20 points for secondary; $p<0.05$). Patients with secondary osteoarthritis had the lowest American Orthopaedic Foot and Ankle Society (AOFAS) scores (32 vs. 38 and 38 points; $p<0.05$). Similar radiographic alignment was found between the three groups ($p<0.05$).

4. PATHOLOGY OF ANKLE OSTEOARTHRITIS

Ankle osteoarthritis is similar to knee and hip osteoarthritis in pathologic findings of subchondral bone changes, such as sclerosis, cyst formation, bone attrition, bone marrow lesions, and osteophytes.[20] Typical histological findings in ankle osteoarthritis include necrotic chondrocytes, irregularity of tidemark, thinning, fragmentation, and fibrillation of thinned cartilage, subchondral cysts with mucoid fluid, and usually no inflammatory findings.[21] The presence of magnetic resonance imaging (MRI)-visible bone marrow lesions may possibly be due to bone marrow necrosis, fibrosis, and trabecular abnormalities. These are usually found in the same area as bone cysts, and there may be an association between these two findings.[22,23] Subchondral cysts contain fibrous connective tissue, adipocytes, and osteoblasts, and may occasionally be continuous with the joint space.[24] In addition, secondary inflammation of the joint may occur.[25,26]

A commonly used histological scale modified for the ankle by Muehleman et al. classifies the degree of cartilage degeneration into four grades: 1) minimal fibrillations, shallow pits or grooves but no changes in articular surface geometry; 2) deep fibrillations and fissuring, flaking, pitting and/or blistering, early marginal hyperplasia and, possibly small osteophytes; 3) extensive fibrillations, fissuring, obvious osteophytes and 30% or less of the articular cartilage surface eroded down to the subchondral bone; 4) prominent osteophytes and greater than 30% of the articular surface eroded down to the

subchondral bone with gross geometric changes.[27]

The pathology of osteoarthritis involves biochemical and matrix-related (catabolism vs. anabolism) factors.[28] Biochemical factors, such as signaling molecules, and matrix-related factors, such as cartilage and proteoglycans, are closely associated with each other.[28] Cartilage is composed of 65 to 80% water and 20% extracellular matrix (collagens, proteoglycans, and glycosaminoglycans).[28] Huch et al. compared cartilage slices from matched knee and ankle joints in terms of DNA content, cell number, proteoglycan, and collagen synthesis.[29] The authors demonstrated that cell density is significantly higher (48% higher; 41,462 vs. 27,949 cells; $p<0.014$) in the ankle joint, and ankle chondrocytes synthesize more proteoglycans and collagens.[29] In a similar study, Kuettner et al. histologically analyzed 507 knee/ankle pairs and 5,239 ankles and identified differences between the cartilage of two joints.[27] Sulfated glycosaminoglycan content was higher and water content was lower in the ankle, which may potentially be responsible for the increased cartilage stiffness and the protection from compressive forces. The higher sulfated glycosaminoglycan content of the ankle cartilage was attributed to the higher synthesis rate when compared to the knee joint (mean, 28,799 vs. 15,510 counts per minute per microgram (cpm/μg); $p= 0.047$).[27]

5. DIFFERENTIAL DIAGNOSES

Patients who present complaining of ankle pain have to be examined closely because there are many structures surrounding the ankle joint that may be the source of pain. These may include the subtalar joint, the peroneal tendon, the Achilles tendon insertion, and others.[30] Therefore, a radiographic finding of talotibio-fibular joint degeneration, which is present in many elderly patients, should not be the only decision-making finding. Ankle osteoarthritis can be diagnosed clinically; therefore, other differential diagnoses must be considered when evaluating the patient. These include inflammatory arthropathies, such as rheumatoid arthritis, infectious mono-arthritis (gonococcal vs. non-gonococcal), gout, and osteonecrosis.[6] A thorough clinical exam, as well as serological inflammatory markers, can help narrow the differential diagnoses. Osteonecrosis may present with symptoms typical of arthrosis before overt joint destruction is observed. Lyme disease is a rare entity associated with this joint. Even rarer phenomena which may affect the ankle joint and present clinically as osteoarthritic pain are sarcoid periarthritis, juxtaarticular benign or malignant neoplasms (or tumors in the synovium or other soft tissues of the joint), myelodysplastic and leukemic disorders which may present as acute arthritis, and plant-thorn synovitis.[30] Some of the other conditions which may result in ankle arthritis include joint dysplasias, acromegaly, Paget's disease, Ehlers-Danlos syndrome, Gaucher disease, Stickler syndrome, hemophilia, hemochromatosis, ochronosis, and neuropathic arthropathy.[6]

6. SYMPTOMS OF ANKLE OSTEOARTHRITIS

Ankle osteoarthritis presents similarly to other joints, with the typical nonspecific symptoms of stiffness, swelling, and pain, typically described as aching within the tibio-talar joint.[31] The pain may be localized or general, may be time and weight-bearing dependent, and in severe disease, may occur at rest and during the night. The diagnosis of ankle osteoarthritis may be clinically determined, without a need for laboratory or radiologic confirmation, especially in the at-risk populations such as age >60 years, female gender, and obesity.[32] Symptoms that are frequently encountered in patients who have ankle osteoarthritis include: joint pain that is activity-related (as the joint fills with fluid), insidious onset with slow progression, exacerbation with weight-bearing, relieved by rest in early stages of the disease, and increasing intensity during the night as the disease progresses. There may be associated morning stiffness, described as being a "deep pain" with "crunching, clicking noises," which may be relieved by heat.[31]

7. PHYSICAL EXAMINATION

The physical exam performed on a patient with ankle pain can help discern when osteoarthritis is the etiology. The patient is asked to wear shorts and remove footwear for adequate exposure. Footwear can then be examined for wear patterns which can indicate abnormal contact of the foot with the ground. Early lateral, proximal, and mid-shoe wear can indicate a supination deformity; while wear on the medial border indicates a pronation deformity.[33] The physical exam then begins with observing the patient's gait. It is important to note if any walking aids are utilized. Inspection of the lower extremity is then performed while the patient is standing with attention given to the overall alignment and then ankle alignment which should be neutral. Inspection of the feet from the side helps to further evaluate for pes cavus or pes planus, while inspection of the posterior ankle is important to view bony bumps like a calcaneal boss.[13] Inspect the ankles with the patient on tiptoes to view ankles turn into varus; this affirms normal motion.[17] With the patient seated, inspection of the ankle and foot follows; with any swelling surrounding the talocrural joint noted along with any localized swelling that could indicate injury. Evaluate for skin discoloration, ulcers, callous, signs of infections, and lack of hair which can signify circulatory changes.[33] Palpation is then performed with focus given to the malleoli, talocrural joint line, Achilles tendon, peroneal tendons, posterior talofibular ligament (PTFL), calcaneofibular ligament (CFL), anterior talofibular ligament (ATFL), and anterior inferior talofibular ligament (AITFL). Ankle osteoarthritis patients typically have tenderness to palpation over the joint line, but care should be provided to perform a full palpation exam to prevent missing other potential pain generators. Further palpation can be performed of the sinus tarsi, calcaneus, cuboid, navicular, talus, posterior tibialis, anterior tibialis, and plantar fascia based on pain location and symptom profile. Ankle motion is then evaluated. Active dorsiflexion, plantarflexion, inversion, and eversion is performed and compared to the other side. Normal ankle dorsiflexion is 0 to 20°, plantarflexion 0 to 50°, inversion 0 to 35°, and eversion 0 to 15°, respectively. Passive motion is then evaluated. Along with dorsiflexion, plantarflexion, inversion, and eversion, evaluation of pronation and supination can be performed passively. In ankle osteoarthritis, range of motion can be limited throughout all planes due to pain, but with increased

restriction of dorsiflexion and plantarflexion. Inversion and eversion is mostly motion of the subtalar joint which can become restricted and painful in conditions of subtalar arthritis and tarsal coalitions.[33] A complete physical exam of the ankle concludes with a lower extremity neurovascular exam along with evaluation of the ipsilateral knee and hip.

8. APPROPRIATE RADIOLOGICAL INVESTIGATION

X-ray findings

Conventional radiographs are usually the next step after physical examination of the ankle.[34] Radiographic investigation includes four weight-bearing standard views: antero-posterior and lateral foot, mortise view of the ankle, and a specialized view of the hindfoot (Saltzman view).[6] For the specialized view of the hindfoot, patients stand on a radiolucent platform facing the film with the medial border of their feet parallel and their knees in extension.[35] A 3mm x 2mm x 6cm lead strip is placed perpendicular to the longitudinal axis of the feet at the most posterior aspect of the heel.[35] The X-ray cassette is positioned at 20° ankle form vertical.[35] Only weight-bearing radiographs should be performed because non-weight-bearing films are often misleading.[6]

In osteoarthritis, radiographs usually demonstrate increased bone density (subchondral sclerosis), flattening of the subchondral surface (bone attrition), and bone marrow lesions. These findings may be due to increased bone turnover and remodeling.[20] It is important to measure radiographic ankle alignment including medial distal tibial and anterior distal tibial angles as well as the apparent movement of the arm in order to continuously monitor for any changes. Several ankle osteoarthritis classification systems have been created including Kellgren-Lawrence,[36] Dijk et al.,[9] Takakura et al.,[37,38] Giannini et al.,[39] Cheng et al.,[40] Cedell et al.,[41] and Krause et al.[38]

Magnetic resonance imaging findings

In some patients, MRIs may be used to identify the early osteochondral lesions that may commonly lead to osteoarthritis.[34] In a study of 78 patients (79 ankles) who had ankle arthritis, Gatlin et al. performed 3.0 Tesla MRIs and arthroscopic examinations with Outerbridge osteoarthritis classifications of the ankles and demonstrated a sensitivity of 0.714 and a specificity of 0.738 for the detection of grades 3 and 4 articular cartilage defects.[42] Other studies have demonstrated similar findings.[43,44] However, standard MRI sequences do not always adequately allow for quantification of early degenerative changes.[45] Quantitative T2-mapping is an MRI technique which can quantify cartilage water content and collagen fiber orientation.[45] Increased T2 relaxation times have been shown to be linked to the development of osteoarthritis.[46] In addition, recently developed three-dimensional isotropic MRI imaging has higher signal-to noise ratio and may better define the stability of osteochondral fragments and provide more information on early changes of cartilage damage.[34] Furthermore, magnetic resonance arthrography can be used to identify cartilage lesions and osteochondral lesions of the tibia and talus.[47]

Computed tomography findings

Computed tomography (CT), specifically, single-photon emission computed tomography (SPECT-CT), may be useful in the evaluation of the extent of the degenerative changes in the ankle joint.[6] In a study of 20 patients with ankle pain, Pagenstert et al. found that the inter-observer reliability for SPECT-CT was 0.86 (95% CI 0.81 to 0.88). Paul et al. performed a SPECT-CT on six consecutive patients who had end-stage ankle osteoarthritis and underwent a total ankle arthroplasty (TAA) and correlated the imaging findings with histological findings at SPECT-positive and SPECT-negative areas of tibial and talar subchondral bone and cartilage.[48] The authors demonstrated increased osteoblast-mediated bone formation ($p=0.011$) in the absence of functional osteoclasts, indicating a pathologic bone-remodeling process in end-stage osteoarthritis.

9. CURRENT TREATMENT OPTIONS AND ALGORITHMS

Search strategies

The literature review was conducted utilizing three electronic databases: PubMed, EBSCO Host, and SCOPUS. This search was performed December 12 to 14, 2017 by two authors (HK and AK). We evaluated studies published between January 1, 1989 and December 31, 2016 using the following search terms: osteoarthritis [title], ankle [title], weight loss [title], physical therapy [title], assistive devices [title], brace [title], orthoses [title], viscosupplementation [title], hyaluronic acid [title], corticosteroid injection [title], biologics [title], stem cell [title], amniotic [title], PRP [title], surgical [title], arthroplasty [title], and arthrodesis [title]. Other search terms included: "ankle osteoarthritis treatment", "non-operative treatment", "surgical treatment", "ankle arthritis", "arthodiastasis", and "allograft transplant". We included all relevant reports on non-operative and operative treatment options; non-peer-reviewed literature and manuscripts in languages other than English were not reviewed. We attempted to include as many Level I and II studies; however, all studies thought to be relevant to our topic were included. The initial search resulted in 372 titles (Fig. 2). After duplicate removal (64 studies) and title and abstract screening (255 unrelated reports removed), 53 full-text articles were assessed for eligibility. A total of 16 reports were excluded (nine irrelevant to this topic and seven in languages other than English). Citation lists from all included reports were reviewed and an additional nine studies were identified. This yielded a total of 46 studies, including 16 on non-operative (two physical therapy/weight loss, two braces and orthoses, two corticosteroid injections, one biologic agents, and nine hyaluronic acid) and 30 on operative treatments of ankle osteoarthritis (18 total ankle arthroplasty/arthrodesis, six osteochondral allograft transplant, two arthroscopic treatments, one interposition ankle arthroplasty, and three arthrodiastasis).

Non-operative

Non-operative treatment options can be successful in the early stages of the disease.[49] These include physical therapy, weight loss, assistive devices, pharmacologic treatments, corticosteroid injections, viscosupplementation, and biologic options.[50,49] Most of the studies investigating these treatment options have low levels of evidence. Viscosupplementation is the only treatment option which has been carefully evaluated utilizing randomized clinical trials.

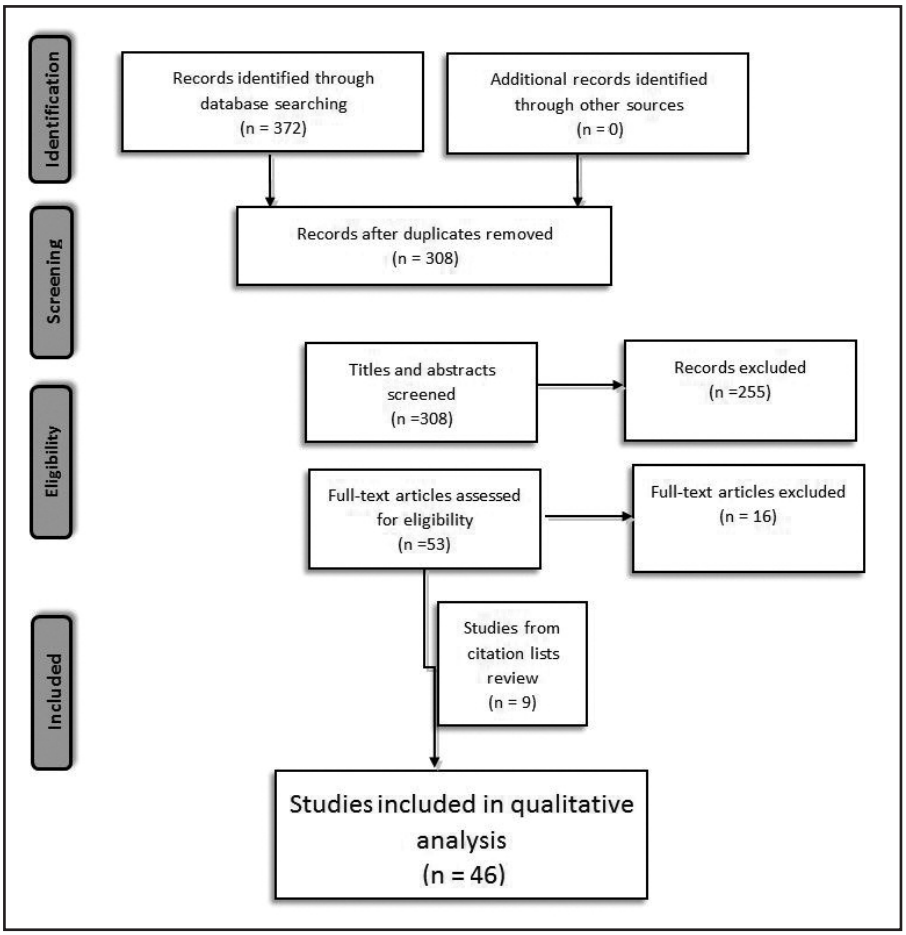

Figure 2. PRISMA flow chart.

Physical therapy, weight loss, and assistive devices

Physical therapy is commonly prescribed as a first treatment option for ankle osteoarthritis. However, it is also important to stress to these patients the importance of weight loss, which is often overlooked. In a study of 142 sedentary, overweight, and obese adults, Messier et al. demonstrated that for each pound of weight lost, there was a four-fold reduction in the load exerted on the knee joint.[51] This load reduction is predicted to be even more marked at the ankle joint.[51] In addition, 25% of body weight can be offloaded from the involved ankle using a single-point cane.[52] In addition to weight loss programs, physical strengthening of lower extremity muscles is important. In a study of 20 patients who had post-traumatic ankle arthritis, Shih et al. demonstrated that gait and muscle strength deteriorated as the disease progressed.[53] Specifically, the dorsiflexor and plantar flexor muscles had decreased strength.[53] Physical therapy and weight loss programs can be prescribed alone or in combination with nonsteroidal anti-inflammatory drugs (NSAIDS) and assistive devices.[54–56]

Two studies have evaluated the use of braces and orthoses in patients who have ankle osteoarthritis,[57,55] (Table I). Wu et al. enrolled 11 subjects into a gait lab study and demonstrated that rocker sole and solid-ankle cushion-heel (SACH) limited forefoot joint excursion during level walking (30 vs. 24°; $p<0.01$), stair climbing, and stair descending, and it decreased ankle motion.[57] In a similar study, Huang et al. performed a gait lab analysis of ankle foot orthoses (AFOs), rigid hindfoot orthoses (HFO-Rs), and articulated hindfoot orthoses (HFO-As), and demonstrated superiority of HFO-Rs in ankle joint motion restriction ($p<0.001$) while allowing for the most forefoot motion.[55,58]

Corticosteroid injections

We found only two studies that investigated the use of corticosteroid intra-articular injections for ankle osteoarthritis (Table I).[59,60] In a study of 12 patients, Ward et al. administered a single 40mg/ml methylprednisolone acetate injection and at one-year mean latest follow up, there was a mean increase in FAOS score of three points.[59] In a similar study, Ali et al. injected a single dose of 40mg triamcinolone in 28 ankles with osteoarthritis.[60] The authors demonstrated that the visual analog score (VAS) decreased from eight points at baseline to six points at the final follow up of six months. These studies have demonstrated that corticosteroid injections can provide short-term symptom relief with minimal side effects, but they have not been shown to stop disease progression.[54,55]

Biological agents

Biologic options include platelet-rich plasma (PRP), amniotic, or stem cells; however, data on these treatment options is limited for ankle arthritis and more prospective randomized clinical trials are needed (Table I).[49] In a study of 20 ankles (20 patients) who had Kellgren-Lawrence stage 2 to 3 ankle arthritis, Fukawa et al. performed two weekly intra-articular injections of 2ml of PRP and demonstrated improvements in VAS pain scores (60 vs. 42 points; $p<0.001$), Japanese Society for Surgery of the Foot (JSSF) scores (52 vs. 66 points; $p<0.001$), and Self-Administered Foot Evaluation Questionnaire (SAFE-Q) scores (47 vs. 56 points; $p<0.001$) at a final follow up of 24 weeks.[61]

Potential role of hyaluronic acid

There are four studies prospectively evaluating the safety and efficacy of hyaluronic acid injections (Table II). In a study of 21 patients who had Kellgren-Lawrence grade II ankle arthritis, Luciani et al. administered three weekly doses of hyaluronic acid. At the latest follow up of 18 months, there was a significant improvement in the mean Ankle Osteoarthritis Scale (AOS) pain score (45 to 34 points; $p<0.05$), AOS disability score (49 to 33 points; $p<0.001$), and VAS pain scores (6.6 to 4.6 points; $p<0.0005$).[62] In a similar study, Mei-Dan et al. performed five weekly ankle injections of hyaluronic acid in patients with Kellgren-Lawrence grade II to IV ankle arthritis with resulting decreases in the mean VAS pain score from 5.29 to 3.05 points ($p<0.001$), and the mean VAS stiffness score from 5.61 to 3.33 points ($p<0.001$).[63] In addition, the patients

Table I
Non-operative treatment of ankle osteoarthritis

Author	Year	N	OA grades	Study Design	Outcomes
Bracing and Orthoses					
Wu et al.[57]	2004	11	N/A	Gait lab analysis of rocker sole and solid-ankle cushion-heel (SACH) heels during level walking, stair climbing, and stair descending.	SACHs limited forefoot joint excursion during level walking (30 vs. 24 degrees; p<0.01), stair climbing, and stair descending and decreased ankle motion.
Huang et al.[55]	2006	13		Gait lab analysis of custom-made ankle-foot orthosis (AFO), rigid hindfoot orthosis (HFO-R), and articulated hindfoot orthosis (HFO-A).	AFO and HFO-R had the most hindfoot motion restriction (p<0.001). However, HFO-R was superior in sagittal plane forefoot motion (p=0.01), and side-slope conditions (p<0.02).
Corticosteroid Injections					
Ward et al.[59]	2008	12	N/A	Single-dose methylprednisolone acetate 40mg/ml. No control cohort. Latest follow up at 1 year.	Mean increase in FAOS of 3 points.
Ali et al.[60]	2016	28	N/A	Triamcinolone 40mg, no control cohort, latest follow up at 6 months.	The mean VAS pain score improved from 8 to 6 points. Five patients had to undergo another injection at 6 months.
Biologic Agents					
Fukawa et al.[61]	2017	20	2 to 4*	Weekly 2ml PRP for 2 weeks. Latest follow up at 24 weeks.	VAS pain scores (60 vs. 42 points; p<0.001), Japanese Society for Surgery of the Foot (JSSF) scores (52 vs. 66 points; p<0.001), and Self-Administered Foot Evaluation Questionnaire (SAFE-Q) scores (47 vs. 56 points; p<0.001).

***Takakura classification system[37]**

experienced improvement in mean ROM by 15° and in the Ankle-Hindfoot Scale score by a mean of seven points.[63] In a study of 93 patients who had Kellgren-Lawrence grade I or II ankle arthritis, Sun et al. administered five weekly doses of intra-articular hyaluronic acid and demonstrated improvements in the mean AOS scores from 1.9 to 2.6 points (p<0.001) and the mean AOFAS score from 64 to 78 points (p<0.001) at the final mean follow up of six months.[64] Local self-limited adverse events occurred in only 6.7%.[64] In a similar study, Sun et al. performed intra-articular injections of hyaluronic acid in 50 patients with Kellgren-Lawrence grade II or III ankle arthritis and demonstrated improvements in the mean AOS score from 5.5 to 3.2 points (p<0.05) and the mean AOFAS Ankle-Hindfoot Score from 60.5 to 76.7 points (p<0.05).[65] In addition, acetaminophen use dropped from 16 to seven tablets/week (p<0.005).[65]

Three prospective randomized controlled trials compared the efficacy of hyaluronic acid and normal saline ankle injections for the treatment of ankle arthritis (Table II). Salk et al. stratified 22 patients who had Kellgren-Lawrence grade II to IV ankle arthritis into five weekly hyaluronic acid or normal saline intra-articular ankle injections.[66] At the final mean follow up of six months, more patients in the hyaluronic acid cohort (five patients) had >30mm of improvement on the AOS scale when compared to baseline (one patient). In a similar study, Karatosun et al. stratified 30 patients (43 ankles) who had Kellgren-Lawrence grade III arthritis into two cohorts: three weekly injections of hyaluronic acid or home-based exercise therapy for six weeks.[67] At the final mean follow up of 12 months, the AOFAS Ankle-Hindfoot Score improved in both groups from baseline (hyaluronic acid 62 to 90 points, p<0.001; exercise 72 to 88 points p<0.001), but no difference between the cohorts at the final follow up was demonstrated.[67] Similarly, DeGroot et al. stratified 56 patients who had Kellgren-Lawrence grade II to IV ankle arthritis into two cohorts: single 2.5ml injections of hyaluronic acid or normal saline.[68] At the final mean follow up of 12 weeks, the overall group of patients demonstrated improvements in AOFAS (p=0.006) and AOS (p=0.013) scores; however, there was no significant difference between the two cohorts (p>0.05).[68]

Three studies compared various dosages and regimens of intra-articular hyaluronic acid injections (Table III).[69,70,71] Mei-Dan et al. studied 16 patients with stage II, III, and IV osteoarthritis, in which intra-articular injections of 25 mg of sodium hyaluronate were injected into arthritic

Table II
Prospective studies evaluating hyaluronic acid

Author	Year	N	OA grades	Hyaluronic acid administration	Latest follow up	Outcomes
Cohort Studies						
Luciani et al.[62]	2008	21	KL* II	Weekly x 3	18 months	There was a significant improvement in AOS** pain (45 to 34; p<0.05), AOS disability (49 to 33; p<0.001), and VAS pain scores (6.6 to 4.6; p<0.0005) from baseline to 18 months.
Mei-Dan et al.[66]	2010	16	KL II-IV	Weekly x 5	32 weeks	The mean VAS pain score decreased from 5.29 to 3.05, p<0.001. The mean VAS stiffness score decreased from 5.61 to 3.33, p<0.001. Improvement in ROM*** (15 degrees, 20%) and in Ankle-Hindfoot Scale score by 7 points.
Sun et al.[64]	2006	93	KL I or II	Weekly x 5	6 months	The mean AOS score improved from 1.9 to 2.6 (p<0.001). The mean AOFAS score improved from 64 points to 78 points (p<0.001). No significant difference in ROM. Local adverse events occurred in 6.7%. Acetaminophen consumption dropped significantly p<0.001.
Sun et al.[65]	201	50	KL II or III	Weekly x 3	6 months	The mean AOS score improved from 5.5 to 3.2 (p<0.05). The mean AOFAS Ankle-Hindfoot Score improved from 60.5 to 76.7 (p<0.05). Acetaminophen use dropped from 16 to 7 tablets/week (p<0.005). Patients demonstrated improvement in 4 balance tests (p<0.05).
Randomized Controlled Studies						
Salk et al.[67]	2006	22	N/A	HA: Weekly x 5 Control: NS, weekly x 5	26 weeks	At 6 months, more patients in HA group (5 patients) had >30mm of improvement on AOS as compared to baseline (1 patient).
Karatosun et al.[68]	2008	43 (30 patients)	KL III	HA: N=19, Weekly x 3 Control: N=24, Home-based exercise therapy x 6 weeks	12 months	AOFAS Ankle-Hindfoot Score: both groups improved significantly from baseline (HA 62 to 90, p<0.001; Control 72 to 88 p<0.001), but no difference between the cohorts at the final follow up.
DeGroot et al.[69]	2012	56	N/A	HA: Single injection 2.5ml Control: Single injection NS 2.5ml	12 weeks	AOFAS and AOS improved at the final follow up for both cohorts, but there was no significant difference between the two groups.

***KL – Kellgren-Lawrence osteoarthritis grade; **AOS–Ankle Osteoarthritis Score; ***ROM – range of motion**

ankles. There was an improvement of 20% in range of motion after 4-, 8-, 11-, 17-, and 32-week follow ups, as well as a statistically significant reduction in pain measured by visual analog score and ankle-hindfoot scores.[69] Witteveen et al. stratified 26 patients who had stage II arthritis (grade by van Dijk et al.)[38] to receive single injections of hyaluronic acid of 1, 2, or 3ml, or three weekly doses of 1ml.[70] In a similar study, Witteveen et al. stratified 55 patients who had stage II osteoarthritis (van Dijk et al.) into two cohorts: those receiving a single 2ml injection and those receiving two weekly 2ml injections of hyaluronic acid.[71] Overall, the mean VAS pain score decreased from 68 to 34 points (p<0.001). Patients who received one injection had a mean change of -43 vs. -24 points in the other cohort (p<0.001). The mean OA disability score decreased by -28 and -16 points (p<0.008) in the single- and two-injection cohorts. The overall Patient global assessment (PGA) scores

Table III
Comparison of various regimens of hyaluronic acid administration

Author	Year	N	OA grades	Study Cohort	Control Cohort	Latest follow up	Outcomes
Witteveen et al.[70]	2010	26	Dijk et al.	1, 2, 3ml injections of HA	Weekly x3 of 1ml HA	15 weeks	None of the single-dose cohorts experienced a significant decrease in VAS pain scores. The 3 x 1ml-dose group showed decrease (median 29mm at 7 weeks) in pain with activities (p=0.046) and pain at rest (median 10mm at 7 and 15 weeks; p=0.046).
Witteveen et al.[71]	2008	55	Dijk et al.	2mlx1 HA	2ml x2 HA	3 months	Overall, the mean VAS pain score decreased from 68 to 34 (p<0.001). Patients who received 1 injection had a mean change of -43 vs. -24 in the other cohort (p<0.001). The mean OA disability score decreased -27.5 and -15.7 (p<0.008) in single- and two-injection cohorts. The overall patient global assessment (PGA) scores improved from 65 to 35 (p<0.001) at 3 months. The mean PGA scores for the single-injection cohort improved from 55 to 21 (p<0.001) and for the two-injection cohort 42 to 27.2 (p<0.001). The mean SF-36 score improved from 36 to 45 (p<0.001) at 6 months.

improved from 65 to 35 points ($p<0.001$) at three months. The mean PGA scores for the single-injection cohort improved from 55 to 21 points ($p<0.001$) and for the two-injection-cohorts from 42 to 27.2 points ($p<0.001$). The mean SF-36 score improved from 36 to 45 points ($p<0.001$) at a mean of six months.

In summary, patients who present with mild ankle arthritis should be prescribed non-operative modalities beginning with physical therapy, pharmacotherapy, and assistive devices if deemed needed. As the disease progresses, corticosteroid injections may be utilized, however, they tend to provide only limited symptom relief. The most evidence-based non-operative treatment option is viscosupplementation with hyaluronic acid, which may provide longer symptom relief than intra-articular corticosteroids.

Operative Treatment

Total ankle arthroplasty vs. ankle arthrodesis

Many studies have compared the safety and efficacy of ankle arthrodesis (AA) and total ankle arthroplasty (TAA) (Figs. 3 and 4). A recent systematic review by Maffulli et al. compiled 21 level 1 to 3 studies at a minimum mean follow up of six months.[72] The authors demonstrated that although TAA has become an increasingly more common treatment for end-stage ankle osteoarthritis, the revision rates for this procedure are significantly higher than for AA (OR 2.28; 95% CI 1.63 to 3.19; $p<0.0001$). Although, the success of TAA has been improving over the past several years, the authors do not recommend its routine use. Of note, the Coleman Methodology Score for this review was 42.5, demonstrating that the overall mean quality of the studies was poor.[73] Many studies have compared the survivorship, range of motion, functional outcomes, and quality of life in these patients.

One Level II and five Level III studies have reported on the survivorship and failure rates of total ankle arthroplasty (TAA) and the ankle arthrodesis (AA) in

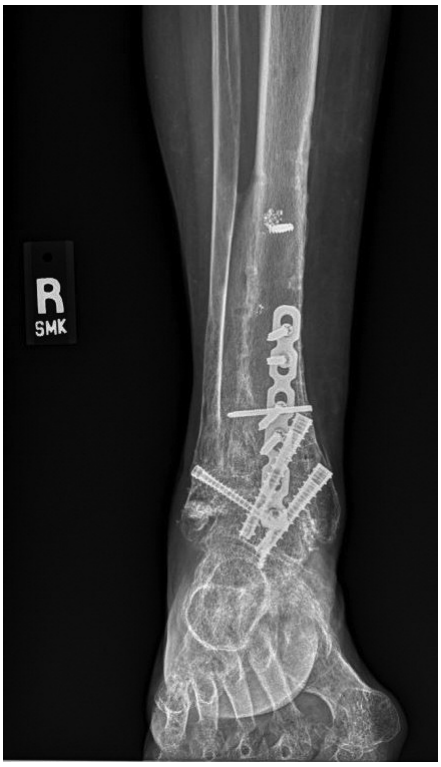

Figure 3. Post-traumatic post-arthrodesis.

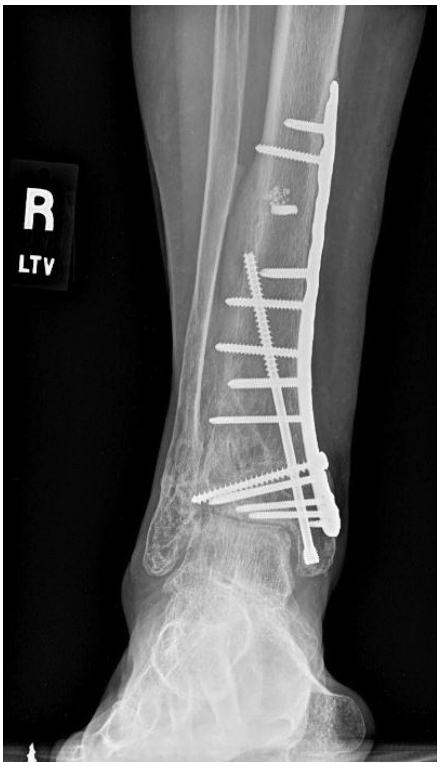

Figure 4. Post-traumatic pre-arthrodesis.

Table IV
Survivorship and failure rates of TAA and AA

Author	Year	Level	N	Follow up (months)	Revision Rates
Survivorship and Failure					
Level II					
Saltzman et al.[74]	2009	II	224	24	12/158 (8%) in TAA and 7/66 (11%) in AA
Level III					
Younger et al.[75]	2016	III	687	57	124/474 (26%) in TAA and 10/213 (5%) in AA
Daniels et al.[76]	2014	III	388	66	48/232 (17%) in TAA and 7/89 (7%) in AA
Krause et al.[77]	2011	III	161	39	12/114 (11%) in TAA and 2/47 (4%) in AA
Saltzman et al.[80]	2010	III	71	50	3/37 (8%) in TAA and 4/23 (17%) in AA
SooHoo et al.[79]	2007	III	5,185	60	23% in TAA and 11% in AA Increased risk of major revision surgery in patients treated with TAA (HR, 1.93, 95% CI, 1.50 to 2.49)
Range of motion					
Jastifer et al.[81]	2015	II	77	12	ROM 18˚ TAA vs 10 ˚ AA
Braito et al.[82]	2014	II	141	6	ROM 17 ˚ TAA vs. 12 ˚ AA
Singer et al.[83]	2013	II	34	12	ROM 18 ˚ TAA vs. 13 ˚ AA
Hahn et al.[84]	2012	II	18	12	ROM 18 ˚ TAA vs. 15 ˚ AA
Rouhani et al.[85]	2012	II	20	22	ROM 23 ˚ TAA vs. 16 ˚ AA
Piriou et al.[86]	2008	II	24	12	ROM 22 ˚ TAA vs. 16 ˚ AA
Functional Outcomes					
Level II					
Jastifer et al.[81]	2015	II	77	12	AOFAS* 81 TAA vs. 72 points AA
Daniels et al.[76]	2014	II	388	66	AOS** 25 TAA vs. 34 points AA
Braito et al.[82]	2014	II	141	6	AOFAS 71 TAA vs. 68 points AA
Singer et al.[83]	2013	II	34	12	AOS 33 TAA vs. 32 points AA
Rouhani et al.[85]	2012	II	20	22	AOFAS 78 TAA vs. 67 points AA
Esparragozza et al.[88]	2011	II	30	25	MFA 37 TAA vs. 40 points AA; p=0.12
Benich et al.[89]	2017	II	273	36	MFA 37 TAA vs. 40 points AA; p=0.12
Level III					
Dalat et al.[90]	2014	III	54	52	AOFAS 70 TAA vs. 62 points AA
Schuh et al.[87]	2012	III	41	35	AOFAS 76 TAA vs. 76 points AA
Krause et al.[77]	2011	III	161	39	AOS 31 TAA vs. 31 points AA
Saltzman et al.[80]	2010	III	71	39	AOS 33 TAA vs. 45 points AA

AOFAS – American Orthopaedic Foot and Ankle Society score; AOS – Ankle Osteoarthritis Scale; MFA – Musculoskeletal Function Assessment; *SF-36 PCS – Short Form-36 Physical Component Score; ** FAOS QOL – Foot and Ankle Outcome Score Quality of Life; BP – Buechel-Pappas score.

patients who had end-stage ankle arthritis (Table IV).[74–80] Overall, four of the six studies demonstrated a higher failure rate in patients who underwent TAA. In addition, SooHoo et al. showed that patients treated with TAA had an increased risk of major revision surgery (Hazard Ratio, 1.93, 95% CI, 1.50 to 2.49).

Several Level II studies have prospectively compared range of motion between patients who underwent TAA or AA (Table IV).[81–86] Not surprisingly, overall, the range of motion was higher in those patients who underwent a TAA.

A total of seven Level II and four Level III studies have evaluated the

Table IV (continued)
Survivorship and failure rates of TAA and AA

Author	Year	Level	N	Follow up (months)	Revision Rates
Quality of Life					
Level II					
Daniels et al.[76]	2014	II	388	66	SF-36 PCS* 37 vs. 39 points
Braito et al.[82]	2014	II	141	6	FAOS QOL** 42 vs. 43 points
Hahn et al.[84]	2012	II	18	12	SF-36 78 vs. 68 points
Esparragozza et al.[88]	2011	II	30	25	SF-36 60 vs. 46 points
Slobogean et al.[92]	2010	II	107	12	SF-6D 0.73 vs. 0.73 points
Saltzman et al.[74]	2009	II	224	24	BP*** function 19 vs. 21 points
Benich et al.[89]	2017	II	273	36	SF-36 38 vs. 40 points; p=0.55
Level III					
Pedowitz et al.[91]	2016	III	68	34	SF-12 PCS 47 vs. 45 points
Dalat et al.[90]	2014	III	54	52	SF-36 63 vs. 56 points
Saltzman et al.[80]	2010	III	71	57	SF-36 33 vs. 45 points

AOFAS – American Orthopaedic Foot and Ankle Society score; AOS – Ankle Osteoarthritis Scale; MFA – Musculoskeletal Function Assessment; *SF-36 PCS – Short Form-36 Physical Component Score; ** FAOS QOL – Foot and Ankle Outcome Score Quality of Life; BP – Buechel-Pappas score.

functional outcomes of patients who had end-stage ankle arthritis and received either a TAA or AA (Table IV).[76–78,81–83,85,87–89] Saltzman et al.[80] performed a study on 71 patients with end-stage ankle arthritis who were treated either with total ankle arthroplasty (n=42) or ankle fusion (n=29). At a minimum two-year follow up (mean 4 years), the total ankle arthroplasty cohort had a higher mean short form mental component (SF-36 MCS) (46 vs 40; p=0.011) score and a lower Ankle Osteoarthritis Scale score (26 vs. 51 points; p=0.001).

There were seven Level II and three Level III studies that assessed the quality of life of these patients (Table IV).[74,78,82,84,88–92] Overall, the majority of reports (five reports) demonstrated better quality of life in patients who underwent a total ankle arthroplasty when compared to those who underwent ankle arthrodesis (four reports).

In summary, the survivorship of ankle arthrodesis has been shown to be superior to total ankle arthroplasty. Although, the range of motion, functional outcomes, and quality of life measures were superior in total ankle arthroplasty patients, the difference was small and does not justify routine use of this procedure in light of high revision rates. Further study in this area is needed.

Osteochondral total ankle allograft transplantation

Several studies have reported on fresh osteochondral total ankle allograft transplantation for the treatment of ankle osteoarthritis (Table V).[93–98] Caravaggi et al. performed a prospective study of 20 patients who either underwent osteochondral allograft transplantation or total ankle arthroplasty.[95] At the mean follow up of five years, both cohorts demonstrated significant improvements in AOFAS scores from baseline (allograft: 75 vs. 53 points; p<0.05; TAA: 80 vs. 29 points; p<0.05). Similar findings were demonstrated in spatio-temporal parameters (stance time, swing time, stride length, cycle time, and speed) (p<0.05). In a similar study, Bugbee et al. performed osteochondral allograft transplantation on 26 ankles with osteoarthritis and, at the mean 41 months of follow up, there were six failures (23%).[97] The mean AOFAS score improved from 27 to 78 points, p<0.0005. The authors demonstrated a significant correlation between low degree of distal tibial slope and better clinical outcomes (p=0.049).[97] Jeng et al. performed total ankle allograft transplantations on 29 patients who had ankle osteoarthritis. At the final follow up of two years, 14 (48%) of the 29 transplants were revised and six (21%) were diagnosed as radiographic failures (allograft fracture, collapse, or progressive joint space narrowing). Several other studies report similar findings.[98,93]

Novel surgical treatment options

Several studies describe arthroscopic synovectomy and debridement of the ankle joint as a potential treatment for osteoarthritis; however, the evidence is lacking.[99,100] This technique appears to be most effective in patients who have ankle impingement.[100] Arthroscopic techniques can also be used for ankle arthrodesis.[101] Several other novel operative techniques have been explored, such as interposition ankle arthroplasty using acellular dermal matrix.[102] In a study of four patients who had end-stage ankle arthritis Carpenter et al. utilized acellular dermal matrix and

Table V
Studies evaluating the outcomes of patients who underwent osteochondral total ankle allograft transplantation

Author	Year	N	OA grades	Study Cohort	Control Cohort	Latest follow up	Outcomes
Caravaggi et al.[95]	2015	20		Osteochondral Allograft Transplantation	Total Ankle Arthro-plasty	5 years	At 5-year follow up, both cohorts demonstrated significant improvements in AOFAS scores from baseline (allograft: 75 vs. 53 points; p<0.05; TAA: 80 vs. 29 points; p<0.05). Similar findings were demonstrated in spatio-temporal parameters (stance time, swing time, stride length, cycle time, and speed) (p<0.05).
Giannini et al. [96]	2014	26		Osteochondral Allograft Transplantation		41 months	There were a total of 6 failures (23%). At the mean follow up of 41 months, the mean AOFAS score improved from 27 to 78 points, p<0.0005). The authors demonstrated a significant correlation between low degree of distal tibial slope and better clinical outcomes (p=0.049).
Bugbee et al.[97]	2013	86		Osteochondral Allograft Transplantation		Mean 5 years	Survivorship was 76% at 5 years and 44% at 10 years. At the latest follow up, the mean Olerud-Molander Ankle Score improved to 61 from 28 points at baseline (p<0.001). However, of the 63 postoperative radiographs available for analysis at the mean of 3.5 years, 29 (46%) were categorized as failures due to >50% joint narrowing.
Berti et al.[98]	2013	10	Grade III	Osteochondral Allograft Transplantation		Mean 14 months	The AOFAS score improved from median of 54 to 77 points (p=0.002). In addition, ankle range of motion in the frontal plane improved from 10 to 13 degrees; p=0.02).
Jeng et al.[94]	2008	29		Osteochondral Allograft Transplantation	N/A	2 years	Success rate was 31% (9 allografts). Patients who had successful allografts had a lower BMI (24 vs. 28; p=0.02) and were older (46 vs. 38; p=0.04).
Meehan et al.[93]	2005	11		Osteochondral Allograft Transplantation	N/A	Mean 33 months	Survivorship was 6 of 11. The mean AOFAS score improved from 55 to 73 points (p=0.01). In addition, pain, gait, and walking scores improved (p<0.05).

demonstrated improved AOFAS scores at the mean 12-month follow up when compared to baseline (35 vs. 89 points; p=0.003). Another treatment option that has been investigated, specifically for post-traumatic ankle arthritis, is arthrodiastasis; however, the evidence for its use is limited.[103–106] This procedure is performed by placing Kirschner wires above (tibia) and below (calcaneus and sometimes talus and metatarsal bones) the ankle joint with external rings tensioned by threaded rods.[107] In a study of 57 patients who had end-stage ankle arthritis, Marijnissen et al. performed a joint distraction arthrodiastasis and demonstrated a 38% decrease in the mean pain score (p<0.0001), 69% increase in mean function score (p<0.0001), and a mean increase in clinical condition of 120% (p<0.0001) at one year follow up.[107] However, several other studies have demonstrated high failure rates (21.7%) and decreased function over time.[106,105]

In summary, current evidence suggests that for patients who have severe ankle arthritis and who have failed non-operative treatment, ankle arthrodesis remains the safest and most efficacious treatment option. However, there have been marked advances in the designs and techniques of total ankle arthroplasty as well as osteochondral allograft transplantation which may be a good alternative for certain patient populations. Other surgical treatment options do not have enough supporting evidence to justify routine clinical use.

CONCLUSION

The incidence of ankle arthritis continues to increase, and it tends to occur in younger patient populations when compared to hip or knee arthritis. Patient work up starts with a careful physical examination and four weight-bearing radiographic views. Advanced imaging options, such as three-dimensional MRI and SPECT-CT, may be useful in early stages of the disease. Early treatment options include physical therapy, pharmacotherapy, and bracing. Corticosteroid injections may be used to temporarily relieve arthritis symptoms. For patients who have moderate to severe disease, surgery may be indicated. However, current surgical treatment

options are either associated with a large number of complications (TAA) or they severely restrict ankle range of motion (ankle arthrodesis), which is undesirable in this young and active patient population. Another non-operative treatment option which can be used in moderate to severe disease is visco-supplementation with hyaluronic acid. This treatment modality has the most evidence-based support and has been shown to be safe and efficacious. STI

AUTHORS' DISCLOSURES

Dr. Chughtai is a paid consultant for CyMedica Orthopedics, Inc., DJO Global, PeerWell, Inc., Performance Dynamics Inc., Reflection Medical Inc., Sage Products LLC, and Stryker.

Dr. Mont is a consultant for, or has received institutional or research support from, the following companies: CyMedica Orthopedics, Inc., Performance Dynamics, Inc., Kolon Pharaceuticals, Inc., PeerWell, Inc., Sage Products LLC, TissueGene, Inc., OnGoing Care Solutions Inc., DJO Global, MicroPort Orthopedics, Inc., OrthoSensor, Inc., National Institutes of Health (NIAMS and NICHD), Stryker, Johnson & Johnson, Pacira Pharmaceuticals, Inc., and US Medical Innovations. Dr. Mont is on the editorial/governing board of the American Journal of Orthopedics, the Journal of Arthroplasty, the Journal of Knee Surgery, and Surgical Technology International. He is a board or committee member of AAOS.

All other authors have no conflicts of interest to disclose.

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