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Advancing Prevention and Treatment of Ankle Osteoarthritis: A Translational Clinical Roadmap from the 2026 AOFAS/ Arthritis Foundation Ankle Arthritis Think Tank

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Abstract

Ankle osteoarthritis (OA) is predominantly post-traumatic in origin. It differs in important ways biologically, mechanically, and clinically from hip and knee OA. Despite recognition of its long-term burden, treatment strategies for ankle OA remain largely reactive and centered on end-stage reconstruction. The Arthritis Foundation and the American Orthopaedic Foot & Ankle Society (AOFAS) co-sponsored an Ankle Arthritis Think Tank to address this deficiency in Napa, CA, on January 22, 2026. The focus was to solve patient frustration of limited treatment options and relatively poor outcomes when comparing to hip and knee osteoarthritis.

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The 2026 meeting brought together a multidisciplinary group of scientists and clinicians to present our current related state of knowledge and to define translational research priorities capable of advancing prevention and treatment of ankle OA within the next decade. Four structured sessions addressed topics relating to ankle OA: (1) Biologic and Biomechanical Pathogenesis, (2) Diagnostic and Management Challenges, (3) Therapeutic Strategies, and (4) Research Methodology. A moderated closing discussion focused on identifying actionable and fundable research pathways. Session presentations and discussion are synthesized here into a unified review.

Keywords: arthritis, ankle osteoarthritis, translational roadmap

Introduction

Ankle osteoarthritis (OA) is distinct from hip and knee OA in its epidemiology, pathophysiology, and patient demographics. Epidemiologic investigations demonstrate that approximately 70% to 80% of ankle OA cases are post-traumatic in origin, most commonly following rotational ankle fracture or chronic ligamentous instability.[1,2] Unlike knee OA, which is frequently age-related and degenerative, ankle OA often develops decades after an initial injury and affects younger, working-age individuals. The ankle joint is characterized by high congruity, thin articular cartilage, and concentrated contact forces. Even small degrees of malreduction or instability can substantially alter contact mechanics. These biomechanical characteristics, combined with the biologic response to intra-articular trauma, create a unique disease process that cannot be directly extrapolated from other large joints.

Although advances have been made in understanding ankle arthritis, the patient experience is largely unchanged since the prior Think Tank proceedings published in 2022.[3,4] The 2026 AOFAS/Arthritis Foundation Ankle Think Tank convened a group of multidisciplinary investigators with the explicit goal of identifying translational targets capable of meaningfully altering the natural history of ankle OA within the next 5-10 years. The present manuscript synthesizes the scientific proceedings and closing discussion into an integrated research roadmap.

Session 1: Biologic and Biomechanical Pathogenesis in Ankle Osteoarthritis

Presenters: Lew C. Schon, MD; William R. Ledoux, PhD; Mitchell C. Coleman, PhD; Kelsey H. Collins, PhD (Moderator: Donald D. Anderson, PhD)

Synovial inflammation and inflammatory mediators. Synovial inflammation plays a central role in ankle arthritis, with pathology varying across its different subtypes. Histologic analyses demonstrate greater lining layer hyperplasia and cellularity in rheumatoid arthritis than OA, with post-traumatic OA (post traumatic arthritis (PTOA)) demonstrating intermediate features.[5] Even mild synovitis impairs cartilage repair capacity by suppressing chondrocyte glycosaminoglycan production.[6] Profiling of synovial inflammatory mediators demonstrates associations with pain and disease stage. Inflammatory mediators implicated in ankle OA include tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, complement proteins, nitric oxide, reactive oxygen species, and eicosanoids.[7] Although biologics effective in treating rheumatoid arthritis have shown limited success in treating OA, nonpharmacologic approaches such as low-intensity pulsed ultrasound reduced synovial macrophage infiltration, suppressed IL-1β, and improved histologic OA scores in preclinical models.[5] Although more research is needed, targeting the fibrosis within the synovium may be a focus of pharmaceutical intervention.

Mitochondrial dysfunction in post-traumatic OA. Preclinical data have shown that rapidly progressive post-traumatic OA in ankle cartilage begins with chondrocyte mitochondrial responses to intra-articular injury. Using a reproducible intra-articular fracture model in skeletally mature Yucatan minipigs, rapidly progressive post-traumatic OA was dependent on dysfunctional mitochondrial over the first 12 hours after injury.[8] This dysfunction preceded structural cartilage degeneration, and blocking mitochondrial damage prevented rapid OA progression. Multiple interventional drug classes, including thiol antioxidants and electron transport inhibitors, mitigated early mitochondrial damage when administered within this early window, supporting the concept that PTOA progression is modifiable shortly after injury.[8]

Adipose tissue and pain-structure dissociation. Adipose tissue is increasingly recognized as an active regulator of joint biology.[9] Leptin signaling was shown to be required for spontaneous OA development independent of body mass.[10] Multi-omics approaches identified adipose-derived mediators influencing cartilage structure and pain. Complement factor D emerged as a key mediator, with restoration reversing cartilage protection in knockout models.[11] Translational studies, including the IDEA trial, demonstrated that metabolomic signatures—particularly eicosanoids—identified pain phenotypes and correlated with clinical improvement following weight loss interventions.[11,12] It remains unknown how systemic inflammatory factors and multi-morbidity may mechanistically affect ankle structure or pain, but this is an area for future study.

Ankle biomechanics and joint function. The highly congruent mortise-and-tenon anatomy of the ankle creates unique biomechanical demands. Advanced imaging has revealed similar talar kinematics in controls, untreated arthritic ankles, and ankles following total ankle replacement (TAR), except for reduced dorsiflexion in late stance for TAR compared with controls.[13] Cadaveric gait simulations demonstrated that implant malalignment significantly alters joint mechanics.[14] Longitudinal clinical trial data showed durable pain relief and functional improvement following both ankle arthrodesis and arthroplasty, with slightly superior functional outcomes following arthroplasty.[15]

Session 2: Diagnostic and Management Challenges in Ankle Osteoarthritis

Presenters: Scott J. Ellis, MD; Amy L. Lenz, PhD; Cesar de Cesar Netto, MD, PhD; Constantine A. Demetracopoulos, MD (Moderator: C. Thomas Haytmanek, MD)

Underestimation of low-energy rotational injuries. Ankle OA differs fundamentally from hip and knee OA in both epidemiology and pathophysiology. Although hip and knee OA are predominantly primary and degenerative in nature, ankle OA is largely post-traumatic. In the seminal series by Saltzman et al,[3] 70% of ankle OA cases were post-traumatic, compared with only 7% classified as primary arthritis. Within this cohort, ankle fractures accounted for 26% and ankle sprain/instability for 19.7% of cases.[3] These findings have been reproduced in subsequent work. Valderrabano et al[4] reported 78% of ankle OA cases were post-traumatic, with ankle fractures (39%) and instability (16%) representing the most common antecedent injuries. Studies examining the role of ankle arthroscopy concurrently with ankle instability and rotational ankle fractures show a high rate of intraarticular pathology. Cartilage injury or osteochondral lesions have been reported at the time of lateral ligament repair in 40.3% to 55% of patients.[16,17] Furthermore, in operatively treated ankle fractures, cartilage injury has been observed in 60% to 80% of cases.[18-21]

Despite these established data, low-energy rotational injuries—particularly Weber B fractures and recurrent ankle sprains—are frequently treated as benign conditions. However, longitudinal clinical data suggest otherwise. In a systematic review of 31 studies, up to 33% of patients reported persistent pain 1 year after ankle sprain, with chronic instability rates ranging from 3% to 34%.[22] Similarly, elite athletic cohorts demonstrate recurrence rates exceeding 17%, underscoring the persistent biomechanical consequences of ankle sprain.[23,24]

A recent single-center retrospective analysis further reinforces this concern. In a review of 491 patients undergoing ankle arthrodesis or total ankle arthroplasty over a 20-year period, 81% of cases were post-traumatic in origin.[25] Within this population, ankle fractures and sprains together accounted for approximately 60% of all end-stage ankle OA. Importantly, the mean interval between initial injury and end-stage arthritis was 17 years, with ankle fractures averaging 18 years and ankle sprains 24 years before definitive surgery. More recently, these single institution findings have been replicated in a multi-institutional retrospective study.[26] These findings suggest that the natural history of low-energy rotational injuries may include a prolonged but progressive course toward degenerative joint disease.

Syndesmotic and deltoid instability: The hidden injury. Traditional classification systems, including Lauge-Hansen, emphasize bony injury patterns; ligamentous injury may be underappreciated. Lauge-Hansen originally suggested that when bone fractures, ligaments remain intact.[27] Contemporary imaging and arthroscopic data challenge that assumption. Hintermann demonstrated that patients with chronic instability frequently exhibit multi-ligament injury patterns, including involvement of the deltoid ligament and syndesmosis.[28] In patients with symptomatic chronic instability, syndesmotic involvement was identified in more than half of cases, and osteochondral lesions were common.

Advanced imaging studies further question reliance on static radiographic parameters. Krähenbühl et al[29] demonstrated that isolated ligament sectioning in cadaveric models does not reliably produce measurable widening on weight bearing computed tomography (WBCT) unless external rotation torque is applied. Similarly, Hagemeijer et al[30] demonstrated that unilateral syndesmotic instability is best appreciated using rotational stress protocols rather than static imaging. WBCT-based volumetric and area measurements have also been proposed to improve diagnostic accuracy. Bhimani et al[31] showed that injured syndesmotic area measurements were significantly increased compared with the contralateral side. Collectively, these findings suggest that syndesmotic and deep deltoid injuries may be present even in fractures traditionally considered "stable," potentially contributing to long-term talar malalignment and progressive cartilage degeneration.

Posterior malleolus and syndesmotic reduction. The role of the posterior malleolus in syndesmotic stability has received increasing attention. Gardner et al[32] demonstrated that in pronation–external rotation injuries with posterior malleolar fractures, the posterior inferior tibiofibular ligament remains attached to the fracture fragment in 100% of cases. Miller et al[33] subsequently showed that fixation of the posterior malleolus improves syndesmotic reduction compared with trans-syndesmotic screw fixation alone, with more accurate reduction demonstrated on postoperative CT. These data suggest that direct restoration of posterior malleolar anatomy may be superior to indirect syndesmotic stabilization, and

malreduction—particularly rotational malreduction—may be a key modifiable risk factor for post-traumatic ankle OA.

Weightbearing CT and three-dimensional analysis. Two-dimensional radiographs incompletely represent the multiplanar complexity of ankle and hindfoot alignment. WBCT has enabled 3-dimensional visualization of joint alignment under physiologic load. Lenz et al[35] demonstrated that statistical shape modeling (SSM)[34] applied to WBCT data can identify population-level morphologic variations associated with specific OA phenotypes. Using SSM, isolated tibiotalar OA was associated with higher calcaneal inclination and cavus alignment, whereas subtalar OA exhibited greater hindfoot valgus alignment. Further computational modeling revealed fibular positional shifts in tibiotalar OA compared with controls, raising the hypothesis that subtle fibular malreduction or chronic instability may predispose to asymmetric joint loading.[35] In a multi-institutional cohort evaluating pilon fractures longitudinally, shape modeling identified hindfoot morphology differences between patients with mild and severe post-traumatic OA at 18 months.[36] These findings suggest that foot type and subtalar morphology may influence progression of tibiotalar degeneration. Such modeling may eventually enable predictive identification of high-risk morphologies and inform joint-preserving interventions.

MRI advancements in cartilage and subchondral bone assessment. Magnetic resonance imaging (MRI) has evolved significantly in the evaluation of ankle cartilage and subchondral bone. High-resolution fast spin echo (FSE) proton density sequences demonstrate excellent sensitivity (94%) and specificity (99%) for cartilage defects in the ankle.[37-39] These non-contrast techniques provide an "arthrographic effect" without invasive injection. Subchondral bone marrow edema, commonly observed following ankle trauma, correlates strongly with pain. Felson et al[40] demonstrated that bone marrow edema was present in 77.5% of patients with pain compared with 40% without pain. Although many contusions resolve, persistent marrow signal abnormalities may reflect altered trabecular mechanics and increased shear stress at the cartilage interface, potentially accelerating degeneration.[41,42] Metal artifact reduction sequences such as MAVRIC (Multi-acquisitional Variable Resonance Imagine Combination) and SEMAC (Slice Encoding for Metal Artifact Correction) further enhance postoperative assessment following total ankle replacement by improving visualization of the bone-implant interface. Together, these imaging advances improve early detection of cartilage injury, subchondral pathology, and postoperative complications.

Prevention of end-stage ankle OA. The data presented in session 2 converge on a central theme: low-energy ankle injuries are common precursors to end-stage OA, yet they are often treated conservatively without detailed ligamentous evaluation or long-term surveillance. Given the prolonged interval between injury and arthritis—often exceeding 15-20 years—there exists a substantial opportunity window for intervention. Improved diagnostic accuracy (WBCT, advanced MRI), heightened suspicion for multi-ligament injury, more anatomic reduction of fractures (including posterior malleolar fixation), and early recognition of syndesmotic instability may alter long-term outcomes. Furthermore, it should be noted that many patients with these low-energy injuries never see a physical therapist or a physician. It is unclear if a standardized physical therapy program protocol may be effective at reducing rates of ankle OA. Prospective, longitudinal studies remain urgently needed to determine whether aggressive early stabilization, physical therapy, ligament repair, or biologic adjuncts meaningfully reduce rates of post-traumatic ankle OA.

Session 3: Therapeutic Strategies in Ankle Osteoarthritis

Presenters: Nancy E. Lane, MD; Jason M. Wilken, PT, PhD; Annunziato Amendola, MD; Anish R. Kadakia, MD; Erik Wikstrom, PhD (Moderator: Jonathon Backus, MD)

Cartilage repair and skeletal stem cells. Efforts to restore articular cartilage have historically yielded inconsistent results. Preclinical investigations have demonstrated that skeletal stem cells, distinct from broader mesenchymal stem cell populations, possess lineage-specific potential for cartilage and bone formation.[43] In murine and porcine models, marrow stimulation combined with vascular endothelial growth factor inhibition (VEGFi) and bone morphogenetic protein-2 (BMP-2) enhanced cartilage formation under hypoxic conditions.[44] However, this regenerative effect diminished in aged animals, limiting translational applicability. Subsequent mechanistic work identified CCN3 as a downstream mediator capable of directing skeletal stem cell differentiation.[45] In aged murine models, the combination of VEGFi and CCN3 restored cartilage formation following microfracture.[45] Although human data are not yet available, these findings support a strategy of biologically augmenting marrow stimulation rather than relying on microfracture alone.

Synovial inflammation and IL-1 inhibition. Synovial inflammation contributes significantly to cartilage degradation in OA.[46] Interleukin-1 (IL-1) is a key cytokine driving catabolic activity within the joint.[47] Observational findings from large cardiovascular trials demonstrated reduced joint replacement rates among patients receiving IL-1 receptor antagonism, suggesting potential structural benefit.[48] Intra-articular gene therapy strategies aim to deliver IL-1 receptor antagonist (IL-1Ra) locally, creating sustained intra-articular cytokine suppression.[49] This is achieved by high-capacity adenoviral vector–mediated inducible IL-1Ra expression or

direct intra-articular IL-1Ra gene transfer without inducible promoter control. Early-phase clinical studies demonstrate significant reductions in WOMAC pain scores sustained up to 104 weeks, particularly in steroid-pretreated cohorts.[50] These approaches may represent a shift toward disease-modifying biologic therapy in ankle OA.

Radionuclide and external radiation approaches. Radiosynoviorthesis and low-dose external beam radiation therapy have been explored as methods to suppress synovial inflammation. Experimental and retrospective clinical data suggest reductions in inflammatory mediators and short-term pain improvement.[51,52] However, long-term structural outcomes and safety profiles require further investigation.

Mechanical load modulation and dynamic orthoses. Elevated articular contact stress following intra-articular fracture is strongly associated with post-traumatic OA development.[53,54] Even modest increases in contact stress substantially increase long-term risk. Custom dynamic carbon fiber orthoses have demonstrated clinically meaningful reductions in pain (up to 60%) and improvements in function among patients with post-traumatic ankle pathology.[55] Biomechanical modeling and cadaveric testing confirm reductions in joint reaction force and peak contact stress of approximately 20% with appropriately designed orthoses.[56-58] These findings suggest that load-modulating orthoses may serve as a non-pharmacologic disease-modifying intervention by shifting patients below biomechanical thresholds associated with OA progression.[54] Prospective long-term clinical outcomes data are needed in this context.

Joint-preserving surgical strategies. Arthroscopic debridement has limited benefit for diffuse ankle OA but remains appropriate for focal osteochondral lesions of the talus.[59] Concerns regarding subchondral bone injury have tempered enthusiasm for microfracture in other joints.[60] Alignment assessment and correction remain essential components of joint-preserving treatment. For large osteochondral defects, osteochondral allograft transplantation remains a viable joint-preserving option. Long-term follow-up demonstrates sustained clinical improvement in selected patients, although failure rates increase over time.[61] Careful patient selection and alignment correction are critical to optimize outcomes. Ankle distraction arthroplasty demonstrated short-term clinical improvement in early randomized trials.[62,63] However, intermediate-term follow-up revealed declining survivorship, with a substantial proportion of patients progressing to arthrodesis or arthroplasty.[64] Early clinical response appears predictive of longer-term success.

Total ankle arthroplasty vs arthrodesis. The contemporary debate between total ankle arthroplasty (TAA) and ankle arthrodesis (AA) centers not on motion alone, but on survivorship, failure mechanisms, adjacent joint implications, and revision pathways. TAA preserves tibiotalar motion and may confer modest functional advantages in early follow-up.[65,66] Fusion provides durable pain relief with low revision rates but eliminates tibiotalar motion and alters hindfoot biomechanics.[15,67] Although radiographic adjacent joint degeneration after fusion is common, symptomatic progression requiring secondary fusion appears substantially lower.[68,69] Registry data demonstrate higher revision rates for TAA compared with fusion at 10 and 20 years.[70,71] Survivorship of contemporary TAA designs continues to improve but remains inferior to hip and knee arthroplasty benchmarks.[72]

Rehabilitative and physical therapy. Physical therapy, particularly for ligamentous injuries, are effective at improving a breadth of biomechanical and patient-oriented outcomes[73,74] and reduce the risk of recurrent ligamentous injury.[75] Modifiable biomechanical variables that are improved with therapy are also associated with deleterious changes in cartilage composition in those with chronic instability, highlighting therapeutic targets for rehabilitative specialists.[76-79] Yet, there is a need for better patient and provider education regarding the benefits of rehabilitative care. Specifically, the vast majority of ligamentous injury patients do not receive referrals to physical therapy,[80] and even fewer patients attend physical therapy.[81] Further, it remains unknown what specific protocols are being used when in-person physical therapy is sought, and there are no data on which outcomes are being consistently measured across institutions. Although in-person physical therapy is effective, there is room for improvement as provider knowledge of key ankle instability impairments and best practice recommendations remains poor[82] despite multiple iterations of for both postoperative[83] and conservative rehabilitation[84] being published.

Given the heterogeneous presentation of impairments following foot and ankle injury, as well as the vast number of modalities and therapeutic exercises that can be deployed to achieve a singular therapeutic goal, it is unlikely that a standard one-size-fits-all rehabilitation protocol will be broadly effective. Indeed, there are more rehabilitation combinations than can be reasonably evaluated through systematic clinical trials. Therefore, the development and implementation of core outcome sets for ankle sprains and chronic ankle instability should be prioritized. This key piece of infrastructure, coupled with rehabilitative plans from across institutions, would allow for the development and analyses of large data sets with potential to elucidate the most meaningful therapeutic domains (eg, neuromuscular control) and if more specific processes (eg, specific balance progressions and/or treatment volumes) are important in achieving key therapeutic targets.

Session 4: Research Methodology in Ankle Osteoarthritis

Presenters: Kenneth J. Hunt, MD; Bopha Chrea, MD; Judith F. Baumhauer, MD, MPH; Todd O. McKinley, MD (Moderator: Constantine A. Demetracopoulos, MD)

Translational basic science in AO. Distinct molecular signatures differentiate ankle OA from knee OA, particularly in post-traumatic disease.[85] Emerging transcriptomic analyses suggest that early post-traumatic ankle OA may be characterized by extracellular matrix remodeling and Wnt signaling activation rather than a predominantly inflammatory cytokine profile. Identification of molecular drivers, including Wnt pathway mediators such as Wnt7b, may provide future disease-modifying targets. Successful clinician-led basic science requires a focused clinical question, strong partnership with basic scientists, institutional support, and progressive funding strategies. The ultimate goal is a collaborative approach to identifying therapeutic or preventive targets and studying the impact of modifying or preventing progression of arthritis in the ankle trauma population.

Advanced biomechanical and imaging investigations. Advances in WBCT, statistical shape modeling,[34] discrete element analysis,[86] and biplanar fluoroscopy[87,88] have shifted ankle research from static radiographic evaluation to functional and computational assessment.[36] These techniques enable physiologic joint loading analysis and in vivo kinematic measurement without soft tissue artifact. Spatiotemporal plantar pressure mapping further enhances gait analysis by normalizing load progression through stance, improving cross-cohort comparisons.[89] Multiscale modeling integrating gait, joint forces, and cartilage contact mechanics provides a framework for understanding mechanical contributors to post-traumatic OA.[90]

Designing better clinical trials in ankle arthritis. Patient priorities consistently emphasize pain and physical function as primary outcomes in ankle OA, but foot and ankle publications have too often fallen short in measuring these outcomes.[91] Use of validated patient-reported outcome measures, including PROMIS Physical Function and Pain Interference, supports standardized assessment.[92] Randomized controlled trials in surgery are notoriously difficult to conduct. In their commentary on a recent multicenter randomized controlled trial comparing ankle arthrodesis to ankle arthroplasty, Sangeorzan et al[93] outlined several key challenges inherent to this type of research: standardizing surgical technique, ensuring sufficient surgeon experience, the difficulty of blinding 2 visually distinct procedures, ethical concerns, and reluctance to participate from both surgeons and patients. Although randomized controlled trials remain the highest level of evidence,[94] lower-level evidence can provide essential pilot data. High-quality trials should incorporate assessor blinding, relevant comparators, clear eligibility criteria, surgeon equipoise, long-term follow-up, and implementation science principles to ensure scalability into clinical practice.

Randomized controlled trials and multicenter infrastructure. Translational research targeting mitochondrial dysfunction and reactive oxygen species in post-traumatic OA has progressed from in vitro and animal models[8] to a multicenter phase II randomized controlled trial evaluating intra-articular amobarbital following high-risk ankle fracture. Execution of such trials requires substantial regulatory oversight, funding, and infrastructure. Integration of objective imaging endpoints, including WBCT-based joint space width analysis, alongside patient-reported outcomes strengthens trial design. Established research consortia, such as the Major Extremity Trauma Research Consortium,[95] provide essential support for multicenter execution.

Discussion

The 2026 AOFAS/Arthritis Foundation Ankle Arthritis Think Tank was convened to define translational priorities capable of altering the trajectory of ankle OA within the next decade. Across sessions and the closing discussion, a consistent conclusion emerged: although mechanistic understanding of post-traumatic ankle OA has advanced, clinical translation remains limited. Continued reliance on end-stage surgical reconstruction alone is unlikely to reduce long-term disease burden. Meaningful progress will require earlier risk identification, biologic stratification, and disease-modifying intervention.

Reframing Ankle OA as a Whole-Joint Disorder

A central theme was the need to move beyond cartilage-centric models. Ankle OA is a whole-joint process involving synovium, subchondral bone, capsule, ligamentous structures, neuromuscular control, and systemic inflammatory influences. This broader framework better reflects clinical presentation, in which pain and stiffness frequently exceed radiographic severity. Synovial inflammation warrants particular attention. Although synovitis has been described in both post-traumatic and degenerative ankle OA, its prognostic and therapeutic implications remain incompletely defined. The closing discussion emphasized that synovial biology may help explain the common dissociation between structural degeneration and symptom burden. Incorporating synovial assessment—through imaging, arthroscopic biopsy, or molecular profiling—may refine phenotyping and guide targeted intervention. Within a clinically relevant horizon, synovium-directed strategies represent a plausible disease-modifying pathway.

Timing as a Therapeutic Variable

The timing of intervention following intra-articular injury emerged as a critical translational question. Experimental data demonstrate that mitochondrial dysfunction and oxidative stress occur rapidly after articular trauma and may initiate downstream degeneration. If these early biologic events are causal, the acute postfracture period represents a modifiable window. However, the temporal threshold for irreversibility remains undefined. It is unclear whether the arthritis cascade occurs within hours, weeks, or months after injury, and whether surgical timing, inflammatory clearance, or early mobilization influence long-term joint biology. Addressing these uncertainties will require prospective trauma cohorts integrating serial advanced imaging, biomarker profiling, and standardized rehabilitation.

Moving forward, clearly delineating temporal windows in which interventions to mitigate PTOA are effective will continue to be important. Clinical trials will need to prioritize intervention timing in statistical models of efficacy. Likewise, basic and translational models that survey interventions will need to establish efficacy time windows of new interventions. Finally, precision-based imaging and biomarker response models to interventions that can stratify individual response to types and timing of interventions need to continue to be developed.

Pain Heterogeneity and Clinical Stratification

The discordance between radiographic severity and symptom burden was repeatedly emphasized. Patients with similar structural degeneration often report markedly different pain and functional limitations. This heterogeneity likely reflects interactions among synovial inflammation, subchondral bone remodeling, metabolic phenotype, central sensitization, and psychosocial factors. Patients are most concerned about decreased physical function and increased pain. Addressing these two issues are as meaningful as mechanical joint restoration or joint preservation. These observations have direct implications for trial design. Enrollment based solely on radiographic criteria risks obscuring biologically meaningful subgroups. Precision phenotyping—including inflammatory markers, metabolic profiling, synovial characterization, and validated patient-reported outcomes—may improve therapeutic targeting and statistical power. Stiffness and limited physical function were also identified as undermeasured yet clinically significant domains. Capsular fibrosis and periarticular remodeling may contribute substantially to disability independent of cartilage loss and warrant focused investigation.

Orthobiologics

Orthobiologic injections are widely utilized in ankle OA despite limited high-level evidence. Heterogeneity in preparation methods, dosing, and patient selection has hindered definitive conclusions. The Think Tank acknowledged this practice-evidence gap and emphasized infrastructure development as a pragmatic solution. As an example, The AAOS Orthobiologics Registry (OBR) is a new specialized, multicenter data collection program launched by the American Academy of Orthopaedic Surgeons in collaboration with AOSSM, AANA, DOD to measure the long-term safety, efficacy, and real-world outcomes of biologic therapies (eg, platelet-rich plasma, bone marrow aspirate concentrate) in patients with knee osteoarthritis. In the ankle, the current evidence base appears sufficient to support immediate development of multicenter data collection, placebo-controlled randomized trials with standardized biologic preparation protocols, indication-specific cohorts (eg, ankle osteoarthritis vs osteochondral lesions of the talus), and registry-based longitudinal follow-up. Without more data on the use of orthobiologics, standardization, and rigorous trial design, additional small heterogeneous studies are unlikely to meaningfully advance the current situation. Future randomized studies should incorporate validated patient-reported outcomes, structural imaging endpoints, and clearly defined phenotypes. Without methodologic rigor, orthobiologic adoption will continue to outpace evidence generation.

Advanced Imaging and Predictive Integration

Advances in WBCT, statistical shape modeling, and computational contact stress analysis provide detailed insight into ankle mechanics. Their clinical impact, however, will depend on predictive integration rather than descriptive application. The closing discussion articulated a vision of multimodal data incorporation—integrating imaging, gait analysis, biomechanics, biomarker profiling, and patient-reported outcomes within large multisite data sets. Application of machine learning approaches to such data sets may permit identification of high-risk phenotypes before radiographic degeneration. This predictive framework represents a shift from reactive reconstruction to preventive intervention.

Rehabilitation as an Immediate Opportunity

Rehabilitation was identified as a near-term, high-yield research target. Post-fracture, post–ankle sprain, and postoperative protocols vary widely across institutions, particularly with respect to weightbearing progression, range of motion strategies, and neuromuscular retraining. Furthermore, no accepted standardized outcome measures exist for something as common as an ankle sprain. As a first step, developing this outcome measure would be key to conducting large observational studies to determine promising therapy modalities. Unlike biologic therapies, rehabilitation represents a scalable and comparatively

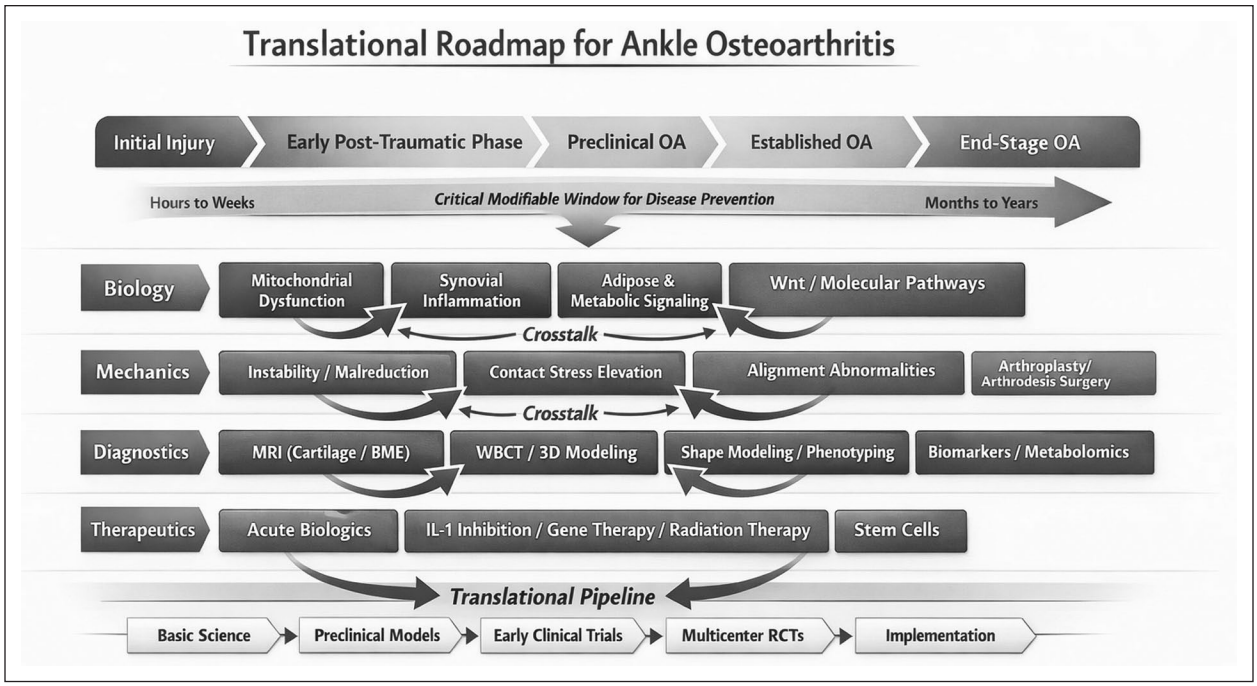

Figure 1. Translational roadmap for revolutionizing ankle arthritis treatment.

low-risk intervention. Ultimately, prospective evaluation of standardized, protocol-driven rehabilitation may yield meaningful improvements in functional recovery and potentially influence long-term joint health.

Collaborative Infrastructure

Cross-disciplinary collaboration was repeatedly emphasized. Ankle OA spans foot and ankle surgery, orthopaedic trauma, rheumatology, pain medicine, rehabilitation science, and translational research. Multicenter infrastructure—particularly collaboration between AOFAS members and trauma research networks—will be essential to conduct adequately powered trials, harmonize imaging protocols, and standardize outcome measurement. Without coordinated infrastructure, translational advances will remain fragmented.

A Roadmap for Moving Forward

Taken together, the themes emerging from the Think Tank are not discrete research priorities, but rather interdependent elements to be addressed as part of a translational pipeline toward revolutionizing ankle OA treatment (Figure 1). The problem of pain heterogeneity underscores why radiographs alone are insufficient—patients with similar structural disease may differ meaningfully in synovial inflammation, subchondral bone response, metabolic profile, neuromuscular function, central pain processing, and functional limitation. That variability, in turn, makes precision phenotyping essential for identifying the right patient, at the right disease stage, for the right intervention. However, meaningful phenotyping will depend on the very infrastructure described throughout this discussion: serial advanced imaging, biomarker and synovial profiling, standardized patient-reported and functional outcomes, harmonized rehabilitation protocols, and multicenter longitudinal data collection. Similarly, questions about timing after injury, orthobiologic efficacy, and rehabilitation response cannot be answered without integrated data sets capable of linking mechanism, structure, symptoms, and treatment response over time. The central opportunity, therefore, is to connect these domains into a coordinated clinical research ecosystem. By doing so, the field can move beyond descriptive characterization and end-stage reconstruction toward predictive models, targeted early intervention, and ultimately disease modification for patients with ankle OA.

A Decade-Scale Clinical Agenda

Within a 5- to 10-year horizon, several priorities were identified as feasible and high impact:

1. Synovium-directed therapeutic strategies in early post-traumatic disease.
2. Prospective evaluation of early mitochondrial-targeted interventions following high-risk fracture.

Table 1. Potential Future Research Focus Areas for Ankle Arthritis.

Domain	Priority Area	Specific Next Steps	Study Design / Approach	Time Horizon	Potential Impact
Biology	Synovium-directed therapies	Define synovial phenotypes (inflammatory vs metabolic vs fibrotic); validate biomarkers	Prospective cohort studies with synovial sampling + imaging correlation	2-5 y	Enables precision phenotyping and targeted therapy
	Mitochondrial dysfunction (early PTOA)	Identify therapeutic window; test mitochondrial-targeted agents post-injury	Multicenter RCTs in acute fracture populations	3-7 y	Disease modification at earliest stage
Mechanics	Early instability and malreduction	Improve detection of syndesmotic/deltoid injury; optimize reduction strategies	Prospective imaging + early surgical technique trials	2-5 y	Reduces long-term mechanical drivers of OA
	Load modulation	Validate orthoses and biomechanical interventions longitudinally	Randomized or pragmatic trials with gait + outcomes	3-7 y	Noninvasive disease-modifying strategy
Diagnostics	Advanced imaging integration	Standardize WBCT, MRI, and shape modeling protocols	Multicenter imaging registries	1-3 y	Improves early detection and risk stratification
	Predictive modeling	Integrate imaging, biomechanics, biomarkers, and PROs	Machine learning applied to large data sets	3-7 y	Identifies high-risk patients before OA onset
Therapeutics	Orthobiologics	Standardize formulations, dosing, and indications; build registries	Registry-based trials + RCTs	2-5 y	Closes evidence-practice gap
	IL-1 inhibition / gene therapy / radiation therapy	Define responder populations; evaluate durability and structural outcomes	Phase II/III randomized trials with imaging endpoints	3-7 y	Establishes disease-modifying treatments
	Cartilage repair and stem cells	Optimize biologic augmentation (eg, VEGF inhibition, CCN3 pathways)	Translational preclinical + early-phase trials	5-10 y	Enhances joint-preserving strategies
Rehabilitation	Protocol standardization	Define optimal weightbearing, ROM, neuromuscular strategies post-injury	Prospective comparative effectiveness trials	1-3 y	Immediately scalable, high-impact intervention
Clinical trials	Trial design optimization	Incorporate PROMIS, imaging endpoints, and biologic stratification	Standardized multicenter trial frameworks	2-5 y	Improves trial quality and interpretability
Infrastructure	Multicenter collaboration	Expand AOFAS + trauma research networks; harmonize data collection	Registry + consortium development	1-3 y	Enables adequately powered studies
Translational integration	End-to-end pipeline	Align basic science with clinical trial design and implementation pathways	Integrated translational research programs	5-10 y	Shifts paradigm from reactive to preventive care

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; PROMIS, Patient-Reported Outcomes Measurement Information System; RCTs, randomized controlled trials; PROs, patient reported outcome measures; ROM, range of motion; VEGF, vascular endothelial growth factor; MRI, magnetic resonance imaging; OA, osteoarthritis; PTOA, post traumatic arthritis; WBCT, weight bearing computed tomography.

3. Biologically stratified orthobiologic randomized trials.
4. Standardization and prospective evaluation of rehabilitation protocols.
5. Multimodal predictive modeling integrating imaging, biomechanics, and biomarkers and patient-reported outcomes.
6. Expansion of cross-society collaborative infrastructure.

Collectively, these initiatives aim to shift ankle OA management from reactionary reconstruction toward earlier identification, risk stratification, and disease modification (Table 1).

Conclusion

Ankle osteoarthritis remains a biologically distinct and clinically heterogeneous disorder that disproportionately

affects a younger population. Advances in mechanistic insight, imaging capability, and collaborative infrastructure provide a realistic opportunity to alter its natural history. Progress will depend on disciplined trial design, precision phenotyping, and coordinated translational execution. The next decade represents a critical window to transition ankle OA care from late-stage salvage toward proactive prevention and early intervention, optimizing the outcomes and function of patients suffering from ankle arthritis.

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