Foot & Ankle Orthopaedics
2022, Vol. 7(4) 1–8

DOI: 10.1177/24730114221127011
journals.sagepub.com/home/fao

Summary Report of the Arthritis Foundation and the American Orthopaedic Foot & Ankle Society's Symposium on Targets for Osteoarthritis Research: Part 1: Epidemiology, Pathophysiology, and Current Imaging Approaches

Jason S. Kim, PhD[1], Annunziato Amendola, MD[2], Alexej Barg, MD[3], Judith Baumhauer, MD, MPH[4], James W. Brodsky, MD[5], Daniel M. Cushman, MD[6], Tyler A. Gonzalez, MD, MBA[7], Dennis Janisse, CPed[8], Michael J. Jurynec, PhD[9], J. Lawrence Marsh, MD[10], Carolyn M. Sofka, MD, FACR[11], Thomas O. Clanton, MD[12], and Donald D. Anderson, PhD[13]

Abstract

This first of a 2-part series of articles recounts the key points presented in a collaborative symposium sponsored jointly by the Arthritis Foundation and the American Orthopaedic Foot & Ankle Society with the intent to survey the state of scientific knowledge related to incidence, diagnosis, pathologic mechanisms, and injection treatment options for osteoarthritis (OA) of the foot and ankle. A meeting was held virtually on December 3, 2021. A group of experts were invited to present brief synopses of the current state of knowledge and research in this area. Part 1 overviews areas of epidemiology and pathophysiology, current approaches in imaging, diagnostic and therapeutic injections, and genetics. Opportunities for future research are discussed. The OA scientific community, including funding agencies, academia, industry, and regulatory agencies, must recognize the needs of patients that suffer from arthritis of foot and ankle. The foot and ankle contain a myriad of interrelated joints and tissues that together provide a critical functionality. When this functionality is compromised by OA, significant disability results, yet the foot and ankle are generally understudied by the research community.

Level of Evidence: Level V - Review Article/Expert Opinion.

Keywords: osteoarthritis, arthritis, ankle, foot, subtalar joint

Introduction

Osteoarthritis (OA) is a serious disease that affects more than 500 million adults, 15% of adults globally, that requires more treatment options to help patients and providers manage the disease.[20,28] Treatments for OA in the foot and ankle have lower satisfaction and less longevity than in other weightbearing joints.[58] The prevalence of OA in the foot and ankle is significant, but unclear because of lack of research.[52,73] A structured search of PubMed shows that there is at least 10-fold more research activity in knee OA compared with foot and ankle OA. Recognizing this need, the Arthritis Foundation (AF), in partnership with the American Orthopaedic Foot & Ankle Society (AOFAS), convened a virtual meeting of academic thought-leaders to

overview the state of science and clinical approaches in OA of the foot and ankle. The goal of the meeting was to highlight the need and encourage further research activity in this area. This article summarizes the workshop presentations and discussions.

Epidemiology and Pathophysiology of Ankle OA

J. Lawrence Marsh, MD

Approximately 1% of adults suffer from ankle OA.[52,75] In the ankle, post-traumatic OA (PTOA) is by far the most common etiology (80%), which is different from the other major lower extremity joints such as knee (10%) and hip (2%).[6,61] PTOA is prevalent and accounts for approximately 12% of symptomatic OA and 5.6 million cases of lower extremity OA in the United States.[6] The burden of ankle OA is high because of the pain and impairment. PTOA occurs at a younger age (approximately 10 years earlier than primary OA), leading to more disability in the productive years of life and providing more challenges to surgical reconstructive options.[35,41] The physical impairment of ankle OA is very significant, having been found to be comparable to that associated with end-stage kidney disease, congestive heart failure, or end-stage hip OA.[22,62]

The most common injuries that lead to ankle OA are sprains, dislocations, and malleolar (rotational) fractures.[32] Significant risk factors at the time of injury for subsequent ankle OA include smoking, high body mass index, and age >30 years.[36,47] The normal ankle forms a relatively tight mortise, and even slight widening of the mortise may lead to instability.[23] Similarly more subtle instability, as from posterior malleolar fractures, can lead to rapid ankle failure if left untreated.[29] Recurrent injury (such as sprains) and chronic instability of the ankle increase the risk for ankle OA.[46] For fractures involving the articular surface of the distal tibia, the role of the location of the fracture is important in dictating the risk for progression to OA. For example, the ankle joint takes higher load in the anterior portion of the joint, so anterior impaction fractures of the tibial plafond have a high risk of progressing rapidly to OA and subsequent joint fusion.[8]

The effects of mechanical injury to the articular surface have been studied in ankle injuries, animal models, and in vitro preparations. The energy of injury in tibial pilon fractures can be measured as an indicator of fracture severity based on computed tomography (CT) data, and it has a strong correlation with the risk for ankle OA. In vitro studies show in osteochondral samples that the severity of mechanical impact to cartilage directly correlates with the amount and progression of chondrocyte death.[72] Malreduction of the fracture can lead to chronic increased joint contact stress, which also increases PTOA risk. Weightbearing CT (WBCT) obtained after the fracture heals can be used to model the increased contact stress and can also assess the joint space width as a measure of early cartilage loss.[3,40]

Imaging of Foot and Ankle Arthritis

Carolyn M. Sofka, MD

A number of imaging modalities are used to evaluate, treat, and follow patients with arthritis of the foot and ankle, including rheumatoid arthritis, psoriasis, gout, and especially the highly prevalent OA.[79] Imaging is used to identify nonuniform joint space narrowing, the presence of osteophytes, sclerosis, proliferative changes, and subchondral cysts.[15,19,33,74] Because of the overwhelmingly frequent posttraumatic nature of OA in the foot and ankle, past trauma must also be considered in imaging evaluation.[24,61] Radiographs, CT, ultrasonography, and magnetic resonance imaging (MRI) are the most frequently used and helpful imaging modalities for OA of the foot and ankle.

Conventional radiography remains the first-line imaging modality being accessible, well-established, reproducible, and inexpensive. The technology can assess bone loss (or

[1]The Arthritis Foundation, Atlanta, GA, USA
[2]Duke University Hospital, Durham, NC, USA
[3]Department of Orthopaedics, University of Utah, Salt Lake City, UT, USA
[4]Department of Orthopaedic Surgery, University of Rochester Medical Center, Rochester, NY, USA
[5]Baylor University Medical Center, Dallas, TX, USA
[6]Division of Physical Medicine & Rehabilitation, University of Utah, Salt Lake City, UT, USA
[7]Department of Orthopaedic Surgery, University of South Carolina, Lexington, SC, USA
[8]National Pedorthic Services, Inc., Milwaukee, WI, USA
[9]Department of Orthopaedics and Human Genetics, University of Utah, Salt Lake City, UT, USA
[10]Department of Orthopedics and Rehabilitation, University of Iowa, Iowa City, IA, USA
[11]Department of Radiology and Imaging, Hospital for Special Surgery, New York, NY, USA
[12]Steadman Phillipon Research Institute, Vail, CO, USA
[13]Department of Orthopedics and Rehabilitation, University of Iowa, Iowa City, IA, USA

Corresponding Author:
Jason S. Kim, PhD, The Arthritis Foundation, 1355 Peachtree St NE, Suite 600, Atlanta, GA 30309, USA.
Email: jkim@arthritis.org

erosions), patterns of joint space narrowing, and proliferative changes. Radiographs can also provide some ability to see bone density. There are limitations when imaging complicated anatomy or overlapping structures, a common occurrence when imaging the foot and ankle and particularly the midfoot. Cartilage cannot be directly visualized, and subclinical erosions cannot be evaluated. Standardized radiographic atlases of features of OA of the foot and ankle are available for scoring research purposes.[45]

CT allows for better evaluation of bone anatomy than radiographs, including joint space narrowing, erosions, and osteophytes. Weightbearing CT (WBCT), when available, affords the ability to evaluate alignment of the foot and ankle in a loaded position.[2,18] Dual-energy CT (DECT) uses 2 detector pairs to obtain 2 separate data sets that can be used to detect urate crystals in suspected cases of gout.[9,21,49,54]

Ultrasonography (or sonography) is useful for soft tissue pathologies such as synovitis or joint effusions.[1,68,77] Power Doppler, available in most ultrasound systems, often correlates with disease activity by indicating presence or absence of blood flow. The Outcome Measures in Clinical Trials (OMERACT) group has worked to standardize definitions and criteria in ultrasonography for erosions, joint effusion, synovitis, tenosynovitis, and enthesitis.[16,70] The sensitivity for detecting erosions by ultrasound is higher than for conventional radiographs. Ultrasonography can be used to complement therapeutic and diagnostic injections as described in the section below.

MRI is the most useful imaging modality for global evaluation of bone and soft tissue of the foot and ankle.[31] With specialized pulse sequences, the modality is capable also of imaging synovitis with and without intra-articular contrast administration, subclinical erosions to follow activity of disease, articular cartilage, and other soft tissue abnormalities, such as tendons or bursal collections.[50] Limitations of MRI include that it is relatively expensive and cannot routinely be acquired with the foot and ankle in a loaded position.

Foot and Ankle Biomechanics and Implications for the Treatment of OA

James W. Brodsky, MD

Patients with ankle OA seek the help of an orthopaedic surgeon when they have trouble with pain, function, or structural deformity. The burden of foot and ankle OA is not purely from the pain caused by synovitis, joint degeneration, or joint damage. Symptoms are distinct to deformity of the structures and alteration of function. The biomechanics of the foot and ankle joints are complex and interrelated, meaning that pain and destruction in some joints are caused by deformities in other joints. Evaluating success in reconstructive surgery of the foot and ankle ideally requires that measures of biomechanical function be collected noninvasively, in real time, in vivo, reproducibly, and objectively.

Gait analysis originated in the 1800s and has significantly advanced because of improvements in technology.[53] Today, multicamera motion capture systems and in-floor force plates are routinely used to rigorously analyze gait. Normal human gait has reciprocal and symmetrical phases; each foot is touching the ground 60% of the time during the "stance" phase and is off the ground 40% of the time in the "swing" phase. When patients lose proper function of the joints in the ankle and feet, there is a remarkable ability to biomechanically compensate,[69] which leads to abnormal gait and increased stress and motion in adjacent joints.

Abnormalities of gait caused by ankle OA can be partially addressed by ankle arthrodesis or arthroplasty.[5,63] However, tibiotalar arthrodesis does not restore normal gait, with persistent alterations in cadence, step length, walking velocity, total support time, and ankle power. After ankle arthroplasty, such functional gait measures do not correlate with patient-reported outcomes such as the visual analog scale (VAS) for pain or the 36-Item Short-Form Health Survey (SF-36) for perceptions of function and improvement. The SF-36 is correlated most with walking speed and ankle push-off power, whereas pain and range of motion are not. When considering arthrodesis or arthroplasty, both are good options that significantly improve pain and function; notably, pain is not caused by the "stiffness" or lack of joint motion, but pain inhibits function. Despite having the joints that move the least in the foot, midfoot OA is a frequent cause of chronic foot pain that deserves further research attention.

Diagnostic and Therapeutic Value of Injections

Daniel M. Cushman, MD

Injections in the foot and ankle serve as a (1) diagnostic tool, to identify the pain generator, or (2) therapeutic, to provide 2-3 months of pain relief. Injections are generally used to augment physical therapy, alleviate milder pain, diagnose the location of pain, and to treat those who are unable to undergo surgical intervention.[17] The most commonly performed injections include corticosteroids (usually with anesthetic), and to lesser degrees the applications of anesthetic only (possibly as a diagnostic), hyaluronic acid, or platelet-rich plasma.

Mixed results have been shown with respect to the predictive nature of pain relief from anesthetic injections in the foot and ankle,[13,43,48,51] which may be related to communication between joint spaces.[7,44] Ward et al[78] showed use of corticosteroid with anesthetic to improve the Foot and Ankle Outcome Score (FAOS) and predict sustained improvement. The study highlights the heterogeneity of

OA, even in the foot and ankle, by observing multiple time points in 36 joints and 18 patients. The field may require further study of the many joints and ligaments to specifically determine the positive predictive value in patients with foot and ankle OA.

Palpation guidance is a standard method to guide injections that is inexpensive, quick, and simple but heavily dependent on the operator.[17] Fluoroscopic guidance is considered the criterion standard because of superior accuracy but is expensive, requires intra-articular contrast, and requires a costly procedure suite.[27] The procedure is operator-dependent, but less so because of the feedback of the contrast flow pattern. Ultrasonography has good accuracy, allows visualization of soft tissue structures, is less expensive compared with fluoroscopy, and can be performed in the doctor's office.[66] Ultrasonography is also heavily operator-dependent. In several studies, ultrasonographic guidance has been found to be comparable to the criterion standard fluoroscopic guidance.[37,42,66]

Platelet-rich plasma (PRP) injections have been considered a promising treatment for ankle (tibiotalar) OA.[56] The high interest is driven by the strong safety profile of PRP and promising results in the knee.[55,57] A recent randomized controlled trial found that intra-articular PRP injections to patients with ankle OA did not significantly improve symptoms or function over placebo in a 26-week period.[57]

The evidence regarding injections in the foot and ankle consists mostly of case series with very few randomized controlled trials.[12,25] Side effects and risks of corticosteroid injections include pain flare (~1/5 patients),[14] infection (~1/10 000 to 1/50 000 patients, or 1/170 physician-years of practice),[11] bruising, nerve injury, and arterial injury. There are many adverse effects of corticosteroids, with main concerns being the disruption of the musculoskeletal, endocrine, and dermatologic systems.[26] There is a lack of evidence for using injections in the foot and ankle, particularly the provocative PRP, and necessitates more research, primarily prospective trials.

Deciphering Pathways Governing Susceptibility to First MTP Joint OA

Michael J. Jurynec, PhD

Although OA is a debilitating disease affecting a large portion of the aged population in the United States, there is not a single drug available that is used to alter the course of the disease.[76] With the exception of surgical intervention such as joint replacement, OA treatment is focused on pain management.[30] Lack of drugs that inhibit progression of the disease is a huge unmet need. Poor understanding of the pathways underlying OA is the key limitation to the development of effective therapies.[60,71] We do not understand the pathways that are critical for the normal homeostatic maintenance of the joint and whose perturbation by gene variants, aging, physiology, environment, or trauma, confer susceptibility to disease. Ongoing research is focused directly on the discovery of molecular and cellular pathways whose normal function acts to limit OA development.

OA of the first MTP joint is the most common form of progressive OA in the foot, affecting 35% to 60% of adults aged >65 years,[34] yet the joint has been largely ignored in genomic studies[4,65] and there are few genes associated with the disease.[39,64] One proven approach toward identifying pathways and biological processes whose normal functions limit disease has been to identify gene variants responsible for highly penetrant familial forms of the disease. Increasing evidence demonstrates there are few differences between the genes contributing to "monogenic" disease and those contributing to complex disease.[10,67] Studying families with first MTP joint OA is a powerful approach to define the genetic factors that contribute to the disease process. A unique medical genetics resource, the Utah Population Database (UPDB), has been used to identify families that segregate highly penetrant, dominant first MTP joint OA. The UPDB provides person-based interlinked records documenting genealogy, medical records, and vital statistics for more than 11 million individuals from the late 18th century to the present.

To date, genomic analysis has been performed on 16 families enrolled with first MTP joint OA. The analyses indicate that alterations in inflammatory signaling are a major risk factor for development of first MTP joint OA. A rare allele of the *Receptor Interacting Protein Kinase 2* (*RIPK2*) gene (p.Asn104Asp) has been associated with dominant inheritance of early-onset OA of the first MTP joint in a single family.[38] The RIPK2 signaling pathway is a component of the innate immunity system involved in clearing bacterial infections and maintaining immune homeostasis.[59] Analysis of additional first MTP joint OA families identified rare variants affecting other components of the pathway, including the upstream activator, NOD2. Introduction of the *RIPK2* disease allele into the mouse genome alters the homeostasis of the joint that previews a definitive OA state and makes the joint more susceptible to injury induced OA.[39] These data indicate that modulation of the NOD/RIPK2 pathway is a general risk factor for first MTP joint OA. NOD/RIPK2 pathway activity may be used for detection of early stages of disease and may also have therapeutic potential. Finally, analysis of additional first MTP joint OA families will define other key genes and pathways that contribute to disease susceptibility.

Conclusions

OA is a complex disease of the joint that affects millions of adults in the United States and worldwide. The OA scientific community focuses much of their attention toward understanding and managing the disease in the knee, hip, and hand. Yet, a substantial number of patients are painfully

disabled by OA in the joints of the foot and ankle, with fewer treatment options with lower satisfaction and longevity. The future can be brighter for these patients and their providers if the broader OA science community can come together to give this neglected area attention and significant expertise. This esteemed faculty of experts sought to provide an overview of the current state of clinical science in OA of the foot and ankle and shared insights for emphasis areas research:

- It needs to be recognized that the anatomy of joints in the foot and ankle is complex, biomechanically robust, and unique.
- Orthobiologics are generally viewed as desirable because of safety and the need to preserve joints in the foot and ankle but have not been found to have consistent benefit.
- Defining the genes and pathways that are significant risk factors for OA in the foot and ankle may help improve understanding of the mechanisms underlying disease onset and progression, development of therapeutics that could modify the course of OA, development of assays to detect biomarkers of early stages of OA, prediction of additional genes that likely contribute to susceptibility, helping to enrich clinical trial populations, and encouraging education and prevention through personalized medicine.

Acknowledgments

The meeting planning committee members and invited speakers are gratefully acknowledged for logistic and technical support. Dr Barg, you will be missed. It was a pleasure and honor to work with you.

Ethical Approval

Ethical approval was not sought for the present study because it is a review article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. ICMJE forms for all authors are available online.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The meeting was convened by the Arthritis Foundation in partnership with the American Orthopaedic Foot & Ankle Society with industry support from Bioventus and Paragon 28.

ORCID iDs

Jason S. Kim, PhD, https://orcid.org/0000-0001-5089-8048
Judith Baumhauer, MD, MPH, https://orcid.org/0000-0003-2142-7778
Daniel M. Cushman, MD, https://orcid.org/0000-0002-4580-1173
Tyler A. Gonzalez, MD, MBA, https://orcid.org/0000-0002-3210-8097
J.Lawrence Marsh, MD, https://orcid.org/0000-0002-3494-6289
Thomas O. Clanton, MD, https://orcid.org/0000-0001-9831-7484
Donald D. Anderson, PhD, https://orcid.org/0000-0002-1640-6107

References

1. Backhaus M, Kamradt T, Sandrock D, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum*. 1999;42(6):1232-1245. doi:10.1002/1529-0131(199906)42:6
2. Barg A, Bailey T, Richter M, et al. Weightbearing computed tomography of the foot and ankle: emerging technology topical review. *Foot Ankle Int*. 2018;39(3):376-386. doi:10.1177/1071100717740330
3. Beardsley C, Marsh JL, Brown T. Quantifying comminution as a measurement of severity of articular injury. *Clin Orthop Relat Res*. 2004;(423):74-78. doi:10.1097/01.blo.0000131637.04391.40
4. Boer CG, Hatzikotoulas K, Southam L, et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell*. 2021;184(24):6003-6005. doi:10.1016/j.cell.2021.11.003
5. Brodsky JW, Kane JM, Coleman S, Bariteau J, Tenenbaum S. Abnormalities of gait caused by ankle arthritis are improved by ankle arthrodesis. *Bone Joint J*. 2016;98-B(10):1369-1375. doi:10.1302/0301-620X.98B10.37614
6. Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma*. 2006;20:739-744. doi:10.1097/01.bot.0000246468.80635.ef
7. Carmont MR, Tomlinson JE, Blundell C, Davies MB, Moore DJ. Variability of joint communications in the foot and ankle demonstrated by contrast-enhanced diagnostic injections. *Foot Ankle Int*. 2009;30:439-442. doi:10.3113/FAI.2009.0439 10.3113/FAI-2009-0439
8. Chohan MBY, Del Balso C, Ching M, Schemitsch E, Lawendy AR, Sanders DW. Impaction fractures of the anterior tibial plafond: outcomes after fractures around the ankle: Is the anterior impaction plafond fracture a problem? *OTA Int*. 2020;3:e076. doi:10.1097/OI9.0000000000000076
9. Choi HK, Burns LC, Shojania K, et al. Dual energy CT in gout: a prospective validation study. *Ann Rheum Dis* 2012;71:1466-1471. doi:10.1136/annrheumdis-2011-200976
10. Claussnitzer M, Cho JH, Collins R, et al. A brief history of human disease genetics. *Nature* 2020;577(7789):179-189. doi:10.1038/s41586-019-1879-7
11. Cushman DM, Christiansen J, Clements ND, Cunningham S, Teramoto M, McCormick ZL. Infections after large joint or bursa injection: a survey of 554 sports medicine physicians. *Am J Phys Med Rehabil*. 2019;98(12):1106-1109. doi:10.1097/PHM.0000000000001255

12. Cushman DM, Ofek E, Syed RH, et al. Comparison of varying corticosteroid type, dose, and volume for the treatment of pain in small- and intermediate-size joint injections: a narrative review. *PM R*. 2019;11:758-770. doi:10.1016/j.pmrj.2018.09.040
13. Cushman DM, Knox J, Kobayashi JK, et al. Does anesthetic relief correspond to future pain relief? A prospective trial examining future pain relief for ultrasound-guided corticosteroid-anesthetic injections. *Am J Phys Med Rehabil*. Published online January 10, 2022. doi:10.1097/PHM.0000000000001959
14. Cushman DM, Kobayashi JK, Wheelwright JC, et al. Prospective evaluation of pain flares and time until pain relief following musculoskeletal corticosteroid injections. *Sports Health*. Published online March 24, 2022. doi: 10.1177/19417381221076470
15. Cushnaghan J, Dieppe P. Study of 500 patients with limb joint osteoarthritis. I. Analysis by age, sex, and distribution of symptomatic joint sites. *Ann Rheum Dis* 1991;50:8-13. doi:10.1136/ard.50.1.8
16. D'Agostino MA, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce—Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open*. 2017;3:e000428. doi:10.1136/rmdopen-2016-000428
17. de Cesar Netto C, da Fonseca LF, Simeone Nascimento F, et al. Diagnostic and therapeutic injections of the foot and ankle—an overview. *Foot Ankle Surg*. 2018;24:99-106. doi:10.1016/j.fas.2017.02.001
18. de Cesar Netto C, Richter M. Use of advanced weightbearing imaging in evaluation of hallux valgus. *Foot Ankle Clin*. 2020;25:31-45. doi:10.1016/j.fcl.2019.10.001
19. Delco ML, Kennedy JG, Bonassar LJ, Fortier LA. Post-traumatic osteoarthritis of the ankle: a distinct clinical entity requiring new research approaches. *J Orthop Res*. 2017;35:440-453. doi:10.1002/jor.23462
20. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. 2004;42:1-9, v. doi:10.1016/S0033-8389(03)00161-1
21. Glazebrook KN, Guimarães LS, Murthy NS, et al. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: initial evaluation. *Radiology*. 2011;261:516-524. doi:10.1148/radiol.11102485
22. Glazebrook M, Daniels T, Younger A, et al. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. *J Bone Joint Surg Am*. 2008;90:499-505. doi:10.2106/JBJS.F.01299
23. Golano P, Vega J, de Leeuw PA, et al. Anatomy of the ankle ligaments: a pictorial essay. *Knee Surg Sports Traumatol Arthrosc*. 2010;18:557-569. doi:10.1007/s00167-010-1100-x
24. Gribble PA, Bleakley CM, Caulfield BM, et al. 2016 consensus statement of the International Ankle Consortium: prevalence, impact and long-term consequences of lateral ankle sprains. *Br J Sports Med*. 2016;50:1493-1495. doi:10.1136/bjsports-2016-096188
25. Grice J, Marsland D, Smith G, Calder J. Efficacy of foot and ankle corticosteroid injections. *Foot Ankle Int*. 2017;38(1):8-13. doi:10.1177/1071100716670160
26. Habib GS. Systemic effects of intra-articular corticosteroids. *Clin Rheumatol*. 2009;28:749-756. doi:10.1007/s10067-009-1135-x
27. Hansford BG, Mills MK, Hanrahan CJ, Yablon CM. Pearls and pitfalls of fluoroscopic-guided foot and ankle injections: what the radiologist needs to know. *Skeletal Radiol*. 2019;48:1661-1674. doi:10.1007/s00256-019-03226-9
28. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*. 2019;37(suppl 120):3-6.
29. Herzog MM, Kerr ZY, Marshall SW, Wikstrom EA. Epidemiology of ankle sprains and chronic ankle instability. *J Athl Train*. 2019;54:603-610. doi:10.4085/1062-6050-447-17
30. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465-474. doi:10.1002/acr.21596
31. Hodgson RJ, O'Connor PJ, Ridgway JP. Optimizing MRI for imaging peripheral arthritis. *Semin Musculoskelet Radiol*. 2012;16:367-376. doi:10.1055/s-0032-1329880
32. Horisberger M, Valderrabano V, Hintermann B. Posttraumatic ankle osteoarthritis after ankle-related fractures. *J Orthop Trauma*. 2009;23:60-67. doi:10.1097/BOT.0b013e31818915d9
33. Huch K, Kuettner KE, Dieppe P. Osteoarthritis in ankle and knee joints. *Semin Arthritis Rheum*. 1997;26:667-674. doi:10.1016/s0049-0172(97)80002-9
34. Iagnocco A, Rizzo C, Gattamelata A, et al. Osteoarthritis of the foot: a review of the current state of knowledge. *Med Ultrason*. 2013;15:35-40. doi:10.11152/mu.2013.2066.151.ai1ofr2
35. International Foot and Ankle Osteoarthritis Consortium, Arnold JB, Bowen CJ, Chapman LS, et al. International Foot and Ankle Osteoarthritis Consortium review and research agenda for diagnosis, epidemiology, burden, outcome assessment and treatments. *Osteoarthritis Cartilage*. 2022;30(7):945-955. doi:10.1016/j.joca.2022.02.603
36. Jaleel A, Golightly YM, Alvarez C, Renner JB, Nelson AE. Incidence and progression of ankle osteoarthritis: The johnston county osteoarthritis project. *Semin Arthritis Rheum*. 2021;51:230-235. Doi:10.1016/j.semarthrit.2020.10.015
37. Jha AJ, Viner GC, McKissack H, et al. Accuracy of talonavicular injection using ultrasound versus anatomical landmark: a cadaver study. *Acta Radiol*. 2020;61:1359-1364. doi:10.1177/0284185120901507
38. Jurynec MJ, Sawitzke AD, Beals TC, et al. A hyperactivating proinflammatory RIPK2 allele associated with early-onset osteoarthritis. *Hum Mol Genet*. 2018;27:2406. doi:10.1093/hmg/ddy196
39. Jurynec MJ, Gavile CM, Honeggar M, et al. NOD/RIPK2 signalling pathway contributes to osteoarthritis susceptibility. *Ann Rheum Dis*. 2022;81(10):1465-1473. doi:10.1136/annrheumdis-2022-222497
40. Kern AM, Anderson DD. Expedited patient-specific assessment of contact stress exposure in the ankle joint following definitive articular fracture reduction. *J Biomech*. 2015;48:3427-3432. doi:10.1016/j.jbiomech.2015.05.030
41. Khlopas H, Khlopas A, Samuel LT, et al. Current concepts in osteoarthritis of the ankle: review. *Surg Technol Int*. 2019;35:280-294.

42. Khosla S, Thiele R, Baumhauer JF. Ultrasound guidance for intra-articular injections of the foot and ankle. *Foot Ankle Int* 2009;30(9):886-890. doi:10.3113/FAI.2009.0886
43. Khoury NJ, el-Khoury GY, Saltzman CL, Brandser EA. Intraarticular foot and ankle injections to identify source of pain before arthrodesis. *AJR Am J Roentgenol*. 1996;167:669-673. doi:10.2214/ajr.167.3.8751679
44. Kirk KL, Campbell JT, Guyton GP, Schon LC. Accuracy of posterior subtalar joint injection without fluoroscopy. *Clin Orthop Relat Res*. 2008;466:2856-2860. doi:10.1007/s11999-008-0236-1
45. Kraus VB, Kilfoil TM, Hash TW 2nd, et al. Atlas of radiographic features of osteoarthritis of the ankle and hindfoot. *Osteoarthritis Cartilage*. 2015;23:2059-2085. doi:10.1016/j.joca.2015.08.008
46. Lofvenberg R, Karrholm J, Lund B. The outcome of nonoperated patients with chronic lateral instability of the ankle: a 20-year follow-up study. *Foot Ankle Int*. 1994;15(4):165-169. doi:10.1177/107110079401500401
47. Lubbeke A, Salvo D, Stern R, Hoffmeyer P, Holzer N, Assal M. Risk factors for post-traumatic osteoarthritis of the ankle: an eighteen year follow-up study. *Int Orthop*. 2012;36:1403-1410. doi:10.1007/s00264-011-1472-7
48. Lucas PE, Hurwitz SR, Kaplan PA, Dussault RG, Maurer EJ. Fluoroscopically guided injections into the foot and ankle: localization of the source of pain as a guide to treatment–prospective study. *Radiology*. 1997;204:411-415. doi:10.1148/radiology.204.2.9240528
49. Mallinson PI, Reagan AC, Coupal T, Munk PL, Ouellette H, Nicolaou S. The distribution of urate deposition within the extremities in gout: a review of 148 dual-energy CT cases. *Skeletal Radiol*. 2014;43:277-281. doi:10.1007/s00256-013-1771-8
50. McQueen F, Lassere M, Edmonds J, et al. OMERACT rheumatoid arthritis magnetic resonance imaging studies. Summary of OMERACT 6 MR imaging module. *J Rheumatol*. 2003;30:1387-1392.
51. Mitchell MJ, Bielecki D, Bergman AG, Kursunoglu-Brahme S, Sartoris DJ, Resnick D. Localization of specific joint causing hindfoot pain: value of injecting local anesthetics into individual joints during arthrography. *AJR Am J Roentgenol*. 1995;164:1473-1476. doi:10.2214/ajr.164.6.7754895
52. Murray C, Marshall M, Rathod T, Bowen CJ, Menz HB, Roddy E. Population prevalence and distribution of ankle pain and symptomatic radiographic ankle osteoarthritis in community dwelling older adults: a systematic review and cross-sectional study. *PLoS One*. 2018;13:e0193662. doi:10.1371/journal.pone.0193662
53. Muybridge E. (1878). *The Horse in motion*. "Sallie Gardner," owned by Leland Stanford; running at a 1:40 gait over the Palo Alto track.
54. Nicolaou S, Yong-Hing CJ, Galea-Soler S, Hou DJ, Louis L, Munk P. Dual-energy CT as a potential new diagnostic tool in the management of gout in the acute setting. *AJR Am J Roentgenol*. 2010;194:1072-1078. doi:10.2214/AJR.09.2428
55. Nie LY, Zhao K, Ruan J, Xue J. Effectiveness of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled clinical trials. *Orthop J Sports Med*. 2021;9:2325967120973284. doi:10.1177/2325967120973284
56. Paget L, Bierma-Zeinstra S, Goedegebuure S, et al. Platelet-Rich plasma Injection Management for Ankle osteoarthritis study (PRIMA): protocol of a Dutch multicentre, stratified, block-randomised, double-blind, placebo-controlled trial. *BMJ Open*. 2019;9:e030961. doi:10.1136/bmjopen-2019-030961
57. Paget LDA, Reurink G, de Vos RJ, Weir A, et al. Effect of platelet-rich plasma injections vs placebo on ankle symptoms and function in patients with ankle osteoarthritis: a randomized clinical trial. *JAMA*. 2021;326:1595-1605. doi:10.1001/jama.2021.16602
58. Paterson KL, Gates L. Clinical assessment and management of foot and ankle osteoarthritis: a review of current evidence and focus on pharmacological treatment. *Drugs Aging*. 2019;36:203-211. doi:10.1007/s40266-019-00639-y
59. Philpott DJ, Sorbara MT, Robertson SJ, Croitoru K, Girardin SE. NOD proteins: regulators of inflammation in health and disease. *Nat Rev Immunol*. 2014;14:9-23. doi:10.1038/nri3565
60. Ramos YF, Meulenbelt I. Implementation of functional genomics for bench-to-bedside transition in osteoarthritis. *Curr Rheumatol Rep*. 2015;17:53. Doi:10.1007/s11926-015-0528-x
61. Saltzman CL, Salamon ML, Blanchard GM, et al. Epidemiology of ankle arthritis: report of a consecutive series of 639 patients from a tertiary orthopaedic center. *Iowa Orthop J*. 2005;25:44-46.
62. Saltzman CL, Zimmerman MB, O'Rourke M, Brown TD, Buckwalter JA, Johnston R. Impact of comorbidities on the measurement of health in patients with ankle osteoarthritis. *J Bone Joint Surg Am* 2006;88:2366-2372. doi:10.2106/JBJS.F.00295
63. Scott DJ, Kane J, Ford S, Daoud Y, Brodsky JW. Correlation of patient-reported outcomes with physical function after total ankle arthroplasty. *Foot Ankle Int* 2021;42(5):646-653. doi:10.1177/1071100720978428
64. Shurnas PS. Hallux rigidus: etiology, biomechanics, and nonoperative treatment. *Foot Ankle Clin*. 2009;14:1-8. doi:10.1016/j.fcl.2008.11.001
65. Sliz E, Taipale M, Welling M, et al. TUFT1, a novel candidate gene for metatarsophalangeal osteoarthritis, plays a role in chondrogenesis on a calcium-related pathway. *PLoS One*. 2017;12:e0175474. doi:10.1371/journal.pone.0175474
66. Soneji N, Peng PW. Ultrasound-guided interventional procedures in pain medicine: a review of anatomy, sonoanatomy, and procedures: Part VI: ankle joint. *Reg Anesth Pain Med*. 2016;41:99-116. doi:10.1097/AAP.0000000000000344
67. Sun BB, Kurki MI, Foley CN, et al. Genetic associations of protein-coding variants in human disease. *Nature* 2022;603:95-102. doi:10.1038/s41586-022-04394-w
68. Swidrowska J, Smolewski P, Stanczyk J, Smolewska E. Serum angiogenesis markers and their correlation with ultrasound-detected synovitis in juvenile idiopathic arthritis. *J Immunol Res* 2015;2015:741457. doi:10.1155/2015/741457
69. Tenenbaum S, Coleman SC, Brodsky JW. Improvement in gait following combined ankle and subtalar arthrodesis. *J Bone Joint Surg Am*. 2014;96:1863-1869. doi:10.2106/JBJS.M.01448
70. Terslev L, Naredo E, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT

ultrasound taskforce-Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open*. 2017;3(1):e000427. doi:10.1136/rmdopen-2016-000427

71. Thysen S, Luyten FP, Lories RJ. Targets, models and challenges in osteoarthritis research. *Dis Model Mech* 2015;8:17-30. doi:10.1242/dmm.016881
72. Tochigi Y, Buckwalter JA, Martin JA, et al. Distribution and progression of chondrocyte damage in a whole-organ model of human ankle intra-articular fracture. *J Bone Joint Surg Am* 2011;93:533-539. doi:10.2106/JBJS.I.01777
73. Trivedi B, Marshall M, Belcher J, Roddy E. A systematic review of radiographic definitions of foot osteoarthritis in population-based studies. *Osteoarthritis Cartilage*. 2010;18:1027-1035. doi:10.1016/j.joca.2010.05.005
74. Valderrabano V, Hintermann B, Horisberger M, Fung TS. Ligamentous posttraumatic ankle osteoarthritis. *Am J Sports Med*. 2006;34:612-620. doi:10.1177/0363546505281813
75. Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of ankle osteoarthritis. *Clin Orthop Relat Res*. 2009;467:1800-1806. doi:10.1007/s11999-008-0543-6
76. Vincent TL. Of mice and men: converging on a common molecular understanding of osteoarthritis. *Lancet Rheumatol*. 2020;2:e633-e645. doi:10.1016/S2665-9913(20)30279-4
77. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum*. 2000;43:2762-2770. doi:10.1002/1529-0131(200012)43:12<2762::AID-ANR16>3.0.CO;2-#
78. Ward ST, Williams PL, Purkayastha S. Intra-articular corticosteroid injections in the foot and ankle: a prospective 1-year follow-up investigation. *J Foot Ankle Surg*. 2008;47:138-144. doi:10.1053/j.jfas.2007.12.007
79. Wilkinson VH, Rowbotham EL, Grainger AJ. Imaging in foot and ankle arthritis. *Semin Musculoskelet Radiol*. 2016;20:167-174. doi:10.1055/s-0036-1581117