Understanding and Restoring Whole Joint Health in Pain Management: An NIH HEAL Initiative Workshop
July 25–26, 2023; Virtual
Full Summary

Overview

This Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, workshop examined the current literature on joint pain research and identified critical knowledge gaps to gain a comprehensive understanding of the whole joint, including the contributions of various articular and periarticular tissue pathologies that lead to pain in different types of joints. Workshop participants examined the relationships and interactions among the tissue components of joints, including myofascial tissues, and their contributions to and impact on reducing pain by preserving and restoring joint health and function.

Five scientific sessions and a final discussion session covered structural changes in joints, mechanisms of whole joint pathology, differences among joint types and joint pain populations, interventions to address joint pain and pathology, and emerging technologies that can be leveraged to advance scientific understanding of joints as complex "organs." The intended audience was interested scientists, clinicians, patients, advocates, and other stakeholders.

(To see the program book and agenda, and to view the recorded workshop, go here: https://www.nccih.nih.gov/news/events/understanding-and-restoring-whole-joint-health-in-pain-management)

Opening Presentations

The HEAL Initiative was launched in 2018 as the National Institutes of Health (NIH's) response to the national crisis of opioid overdose and addiction and untreated pain. The initiative's efforts in pain research include preclinical, translational, and clinical research. In the addiction research space, emphases include new treatments for opioid use disorder, enhancing outcomes for newborns affected by opioid exposure, new prevention and treatment strategies, and translating research into practice. Since 2018, more than 1,000 NIH HEAL Initiative research projects have been launched, including some that focus on joint pain, and more than $2.5 billion has been spent on research. The initiative's research is already making a difference, for example, with a new standard of care for infants born dependent on opioids. But much remains to be done. Chronic pain continues to be a huge, unsolved problem, opioid overdose deaths still occur in large numbers, and investment in the development of new treatments for pain and addiction remains low. Joint health and pain are intricately related in complex ways. In the area of joint health, the NIH HEAL Initiative has three ongoing programs: the Restoring Joint Health and Function to Reduce Pain (RE-JOIN) consortium; the myofascial biomarkers program, which is seeking to understand how pain can be measured in fascial tissues; and the Back Pain Consortium (BACPAC) research program.

The concept of whole joint health is derived from the larger concept of whole person health, which is at the core of the National Center for Complementary and Integrative Health's (NCCIH's) strategic plan. Whole person health involves considering all aspects of a person, including their behavioral, social, and

environmental contexts as well as biology, as they travel along the bidirectional path between health and disease. Similarly, whole joint health involves considering all the connected tissues that contribute to the structure of the joint, including the cartilage, bone, synovium, joint capsule, ligaments, tendons, fascia, and muscles. Different joints share common structures, both articular and periarticular, even though some also have distinctive structural features. People often assume that joint pain comes from the articular tissues, particularly cartilage, rather than periarticular tissues, but this may not be accurate. Pain can originate from the inner components of the joint, but the periarticular tissues, such as myofascial tissues, may also play a role. A multitude of medical, psychological, and social conditions feed into the development of pain and its resolution. Understanding how to intercept pain signals coming from the tissues, such as the joint, is key to diagnosing and treating pain. Understanding the pathology and progression of joint disease could lead to prevention and earlier interventions before the end stage of the disorder.

Structural and Mechanical Factors in Joint Pain

Four presentations focused on joint pain as a multifactorial condition that involves not just the affected joint but also surrounding tissues and their form and function.

***Osteoarthritis Pathobiology*:** Although osteoarthritis (OA) is a whole joint disease, attention has focused primarily on the loss of articular cartilage attributed to "wear and tear." However, the articular cartilage is not directly innervated, suggesting that OA pain originates from other joint tissues. The structural changes of OA and its symptoms involve the subchondral bone, osteophytes, meniscus, synovial membranes, and ligaments, and the infrapatellar fat pad in the knee. Although histological changes involve the cartilage and bone, other tissues also contribute to the joint environment, which contains cytokines, chemokines, matrix metalloproteinases, and growth factors. Abnormal mechanical loads and aging play important roles in OA, activating catabolic and inhibiting anabolic signaling, promoting production of substances that fragment the matrix. Understanding the root causes of these pathways and mechanisms will affect how OA and associated pain might be treated in the future.

***Whole Joint Biomechanical Modeling*:** Computational biomechanical 3-D mapping at the whole joint level has emerged as an essential tool for joint research and care, unraveling the complex nature of joint structure-function-pain relationships. Recently, this technique was used to assess nerve innervation in temporomandibular joint (TMJ) and knee joint pain, mapping nerve endings in the soft tissue to investigate relationships between mechanical stress and pain generation. The model showed that mechanical stress is concentrated in a focal spot, inducing nociceptive impulses. In the future, it may be possible to quantitatively connect structure and function to pain signals through multiscale computational models.

***Structural Damage in OA and Pain*:** The underlying pathologies leading to joint pain cannot be readily determined from radiography alone, requiring consideration of other factors. Imaging modalities such as magnetic resonance imaging (MRI) have shown that various structural alterations such as meniscal tears, subchondral bone marrow lesions, subarticular bone attrition, synovitis, and effusion are related to knee pain. Additionally, changes in bone marrow lesions and inflammatory markers found through MRI are associated with fluctuations in pain in patients with knee OA. It is unclear how much of the variance in pain is accounted for by structural change. Evidence suggests that large bone marrow lesions

are strongly associated with knee pain, followed by synovitis and effusion, and potentially also cartilage volume and thickness. Interpreting these relationships is challenged by uncertainty about whether associations are causal or rather markers of the severity of other structural pathologies that may contribute to pain.

***Subchondral Bone as a Source of Pain*:** Bone marrow lesions in the subchondral bone are largely associated with pain on weight bearing rather than non-weight-bearing pain. This suggests an interaction with biomechanical factors and different mechanisms for different aspects of knee OA pain. Bone marrow lesions are histopathologically complex; they represent heterogenous subchondral pathology in OA, with high metabolic activity and structural change. They may be a biomarker for the actual cause of pain, which is not yet fully understood. Several genes are upregulated in bone marrow lesions, and some are associated with pain, but it is not clear which genes are drivers of pain rather than consequences of bone marrow lesions. Tools are now available to assess how bone marrow lesions cause pain in arthritis, and research in this area may lead to novel treatments.

Comments and Discussion

- OA is often considered one disease, but overwhelming data suggest it is a family of diseases that yield common phenotypic outcomes via different pathways and mechanisms depending on the initiating cause.
- Studies in community cohorts have focused on associations because it is more straightforward than identifying causes. The field needs to move beyond that strategy to focus on causation, particularly for OA pain.
- Linking phenotypes to genotypic markers may help predict individual susceptibility to joint diseases, surgical outcomes, and individual differences in responses to pain treatments.
- The similarities between OA pain and back pain highlight that there is no perfect match between structural changes and suggest the importance of factors beyond the structure itself. However, many of the same factors are involved in both conditions, such as cytokines, proteolytic enzymes, cellular senescence, and neo-innervation.
- The role of synovitis in joint pain is complex because it is not a single indicator. It involves multiple disease manifestations at the structural level in the synovium, including inflammatory infiltrates from systemically derived immune cells. Robust stromal activation that underpins fibrosis may also underpin pain and synovial lining hyperplasia.
- Because research has focused primarily on later-stage joint disease, little is known about early-stage phenotypes, the knowledge about which could inform prevention strategies.
- There are many factors that can contribute to joint pain, including changes to the joint structure, biomechanics, and inflammation. These factors can also contribute to the chronification of pain, with accompanying changes to peripheral and central innervation due to inflammation, reprogramming of synapses, and epigenetic and cognitive changes. Effective pain treatments must consider these factors to address joint pain.

Mechanisms of Whole Joint Pathology

Four presentations focused on mechanisms of pathology, including the myofascial component of joint pain, structural neuroplasticity in joint innervation, the role of adipose tissue and systemic factors in knee joint damage and pain, and intertissue communication.

***Myofascial Component of Pain*:** Muscle has long been considered the quantal element in the control of movement. However, recent research has demonstrated a strong interaction between muscle fibers and intramuscular connective tissue and between muscles and fasciae (collectively called the "myofascial unit"), suggesting that muscle can no longer be considered the only tissue that produces movement. The fascia is a living and sensitive tissue that changes with age, trauma, and other factors, leading to stiffer fascia that can promote an unbalanced load on the joint. This biomechanical aberration may be linked to the development of OA or a worsening of its symptoms. In addition, fascia are well innervated, such that injured fascia produce nociceptive signals that can lead to the perception of pain. The origin of pain in a joint could be misunderstood; the fascia and joint capsule are connected, making it difficult to identify the source of pain.

***Structural Neuroplasticity in Joint Innervation*:** A more complete understanding of the nociceptive innervation of the joint is necessary to aid the development of novel, effective pain therapeutics for OA. To understand the relationship between joint damage and pain, it is necessary to understand where the neurons are located in the joints. Recent research has shown that joint innervation is not static. Abundant neuroplasticity exists in joints in arthritis and perhaps also with aging. To better define the relationships among joints, neurons, and pain, efforts are needed to document the precise anatomy of innervation changes, describing the neuronal subsets, identifying drivers of neuroplasticity, understanding neuroimmune interactions in the joint/nervous system, and understanding phenotype- and sex-specific differences.

***Adipose Tissue Crosstalk and Systemic Factors in Joint Damage and Pain*:** Obesity-induced OA involves both metabolic and biomechanical factors, and a key link is excess adipose tissue. A mouse model of lipodystrophy (LD), in which the animals lack fat but maintain normal body mass, demonstrated that the mice are protected from cartilage damage. After fat was transplanted into LD mice, the mice developed OA, suggesting that adipose tissue and adipokines rather than body weight may be critical mediators of obesity-induced joint degeneration. A multiomic approach that characterized transcriptional factors secreted by adipose tissue in joint fat pads was used to objectively determine which pathways and fat-secreted targets are involved in the reintroduction of cartilage damage and pain. Adipose tissue is necessary for the normal development of muscle mass and strength, and leptin was found to be the key adipokine mediating this regulation. Cartilage injury may induce changes in systemic adipose external to the knee joint, showing a bidirectional crosstalk mechanism that can be harnessed for therapeutic development.

Intertissue Communication: Although some systemic influences on joint tissues have been characterized, the influence of signals from the joint to other organs have not. The intra-articular space is a unique environment where direct tissue-tissue contact, including mechanotransduction and the exchange of soluble messengers, maintains joint homeostasis and generates a "whole joint response" to injury and in disease. Intertissue communication is most evident by the involvement of different joint tissues in response to a primary insult to a single tissue such as cartilage, meniscus, or

tendons and ligaments. In addition, senescent cells have been shown to induce senescence in other tissues. Understanding the communication between damaged tissues and sensory nerves has potential to reveal new targets for pain management. Whole joint maps of cell populations within each tissue with transcriptomes and secretomes in healthy, aged, and diseased human joints are in development to determine senders and recipients of mediators. Mediators of intertissue communication that promote spreading and chronicity of pathogenic signaling across all joint tissues are potentially promising therapeutic targets.

Comments and Discussion

- While OA knee pain is associated with bone marrow lesions and synovitis, in rheumatoid arthritis patients reports of pain are not worse in those with severely inflamed synovium. This raises the question of what is causing pain in patients with low level synovial inflammation, such as pathology in other parts of the joint (e.g., capsule, fascia, tendon, or subchondral bone) or pathology in the synovium that is uncoupled from inflammation.
- A critical component in understanding the complexity of OA pain will involve implementing statistical and computational approaches (e.g., machine learning, artificial intelligence [AI] modeling) to analyze large and diverse high-dimensional data sets. Integration of these complex systems and data streams will provide holistic insights into patient-specific relationships.
- The study of intertissue communication is a key gap in our understanding of joint degenerative diseases. More research is needed to understand communication among the tissues within the synovial compartment and those in the surrounding periarticular areas. Research provides evidence of both intraindividual and interindividual heterogeneity in many measures of tissue health, highlighting the need for a precision approach to joint pain management.
- The heterogeneity of OA has been demonstrated in phenotyping studies measuring pressure, thermal, and mechanical pain sensitivity, as well as conditioned pain modulation. Studies of muscle and fascia stiffness and muscle quality also reveal how changes contribute to sensitization and pain.
- Targeted therapies that do not account for all of the systemic influences affecting joint health may not be able to show sufficient therapeutic benefit.
- Fascial tissue is pervaded by a dense network of nerves. There are differences in the innervation between the two types of fascia. Evidence suggests that they play different roles in proprioception and pain perception, resulting in either regulating the tensions coming from related muscles or coordinating the actions of underlying muscle.
- Tissue cell bodies and nerve endings change over time and with disease or trauma. Studies are needed over the lifespan to understand intra- and interindividual changes. Focusing only on cadaveric tissue or end-stage disease does not provide a complete picture of the disease.
- Data and computer scientists and modelers are needed to assist in developing the techniques to manage and evaluate multiple large, complex, multifaceted datasets. In the interim, much can be learned from combining existing structural, biomechanical, neuroanatomical, physiological, and spatial data.

In addition to addressing multitissue omics and multicompartment integration, attention should also be paid to the impact that phenotypic differences have on joint pathology. The ways in which an

individual's OA progresses is driven in part by the primary disease but also by many external factors such as levels of activity, nutrition, and the choices made, for example, about surgery or other forms of treatment, over the years of disease development and progression.

Differences Among Joint Types and Joint Pain Populations

Four presentations focused on differences found between sexes and among populations in signs, symptoms, and underlying features of joint diseases.

***Heritable Disorders of Connective Tissue as Models for Joint Disease*:** These heritable disorders comprise a widely diverse group of genetic conditions, many of which manifest with joint disease that mirrors that seen in common joint diseases, such as OA and inflammatory arthritis, causing joint pain. The diversity of joint involvement in the more than 500 disorders offers a lens through which one can dissect the contributions of genetics, environment, and gender to differences in joint disease. An atlas of joint involvement in hereditary disorders of connective tissue combined with new animal models will inform understanding of the effects of specific proteins and metabolic pathways that contribute to joint disease. Identifying the precise effects of specific genes on the human skeleton can theoretically aid the formulation of rational therapeutic strategies to address joint pain in the general population.

***Comparing Temporomandibular Joint and Spinal Facet Joint Pain*:** Painful conditions in cervical spinal facet joints and the TMJ provide useful platforms to elucidate the mechanical and molecular mechanisms contributing to synovial joint pain. In both, studies have revealed the combined influence of tissue mechanics, molecular processes, and nociception in joint pain. There are also important differences within an individual and across demographic groups. In healthy joints there are differences in anatomic shape, loading, and innervation. In the pathological joint, structural and biochemical changes can be induced to alter the microenvironment and modify the biomechanics of constitutive tissues. Research has shown collagen breakdown as a hallmark of joint degeneration and possible nerve activation, specifically collagen catabolism and collagenase enzymes, especially the matrix metalloproteinases (MMPs). MMP-1 has been shown to be altered in joint capsules and synovial fluids of painful joints in humans but has not been studied for its effects in mediating joint pain or for its mechanistic relationship with the nociceptive pathways.

***Structure and Function in Spine and the Sacroiliac Joint*:** Many cases of lower back pain originate in the lumbar spine; it is believed that the sacroiliac (SI) joints could be involved in as many as 15 to 30 percent of these cases. As part of the axial skeleton, the spine provides flexibility, transmits load to the SI joint (SIJ), and protects the nerve roots. In comparison, the SIJ is rigid and thus primarily transmits load to the pelvic girdle and then to the legs. The range of motion across the SIJ is only a few degrees. Discs, facets, and ligaments transmit loads in the spine, while the SIJ is the primary structure for load transmission. Shear loads are very high across the SIJ. Pathologic changes and injuries specific to the SIJ that cause pain include capsular and ligamentous tension, hypo- or hypermobility, extraneous compression or shearing forces, micro- or macrofractures, soft tissue injury, and inflammation. Better models are needed to assess SIJ mechanics in males and females with and without pain and across different age groups. Cadaveric and animal biomechanics/histologic studies of SIJs can provide insight into the biomechanics and innervation of degenerated SIJs.

***Differences by Sex and Race in Multiple Joint Osteoarthritis*:** Underrepresented groups in medical research and care, including women and Black individuals, tend to report more pain associated with OA than men or non-Black individuals. Black patients with symptomatic knee OA have poorer function that can be partially explained by differences in socioeconomic status and physical health status. Other factors are associated with higher pain and lower function such as greater pain catastrophizing, reduced psychosocial resilience, and pre-existing health disparities and structural racism. Despite a similar burden of hip OA and a higher burden of knee OA disease prevalence among Black individuals compared to non-Black individuals, strong disparities in treatment continue to exist. The Johnston County Osteoarthritis Project has followed a large and diverse cohort of Black and White men and women for 30 years to obtain insights on patterns of multiple joint OA (MJOA) by race and sex. Based on survey data, this cohort showed that the burden of MJOA was associated with poorer health and physical function. Further analysis found that the number of falls increased with the number of lower extremity joints diagnosed with symptomatic OA and the odds of having a fall within the next 6 years increased.

Comments and Discussion

- Structural damage is particularly relevant in hypermobility. Hypermobility is similar to arthritis in that it does not necessarily equal joint pain, just as OA does not equal joint pain. In terms of neuromuscular dysfunction, hypermobility involves too much range of motion whereas instability is the inability of the neuromuscular structures to control that motion to protect the joint.
- From a drug development perspective, understanding the similarities and difference in pathology, pathophysiology, pain manifestations, and mechanisms among joints across OA progression could lead to systemic, whole joint treatment approaches.
- Many patients have both significant joint-related complaints as well as radiographic evidence of some sort of degenerative or inflammatory process. More study is needed on how treatments such as physical therapy and strategies to optimize joint alignment change the symptomatology of joint-related complaints, for example, based on radiographic or other biomarker effects.
- Immune checkpoint inhibitor therapy offers a model system to look at the joints and joint immunology in that this therapy can cause inflammatory arthritis.
- The complexity of the TMJ is notable when compared to the knee. TMJ disorders are a group of multiple conditions that cause pain and dysfunction involving muscle, cartilage, and synovial tissue, which makes it a complex system for identifying the source of pain and effective treatment.
- Many TMJ disorder patients respond well to osteopathic manipulation (non-clenching, relaxation, treating muscles and fascia, increasing motion of the TMJ, self-stretching); this should be pursued as a more conservative approach.
- Sex hormones are a likely mediator in joint disease as evidenced by differences in signs and symptoms among males and females.

Interventions To Address Joint Pain and Disease

Four speakers presented data on the effectiveness and complexity of various treatment strategies for joint pain, both singular and multimodal.

***Transcutaneous Electrical Nerve Stimulation (TENS) and Pain Control*:** TENS is a nonpharmacologic treatment for pain. Animal models show that TENS produces analgesia through activation of opioid and serotonin receptors in the central nervous system, which subsequently reduces release of excitatory neurotransmitters and sensitization of dorsal horn neurons. However, the clinical literature on TENS is mixed, with reports ranging from significant effectiveness to no effect. Recent studies suggest that factors related to TENS application should be considered when assessing efficacy, such as dosing, interactions with opioid use, the population and outcome assessed, and the timing of the outcome measurement. More recent research that has considered these factors and controlled for bias has provided evidence that TENS reduces movement pain and fatigue and is safe and cost effective.

***Manual Therapy for Lower Extremity OA-Related Joint Pain*:** OA is the most common painful joint disorder of the lower extremity, with the highest prevalence in the knee joint. Placebo-controlled trials have shown that manual therapy is efficacious for knee OA, with comparative effectiveness against other common OA treatments (e.g., exercise, corticosteroid injections). Despite it being cost effective, its use for pain management in OA is low compared to the use of pharmacologic therapies. It is rarely used in advance of knee replacement surgery. Misperceptions about the effects of movement, strength training, and manual therapy on the joint in part explains low uptake.

***Diet and Exercise Interventions and Pain*:** Obesity is associated with joint pain, and the greater the obesity the greater the joint pain. Exercise reduces joint pain in people with obesity and/or knee OA; however, the effect size decreases over time. Thus, despite the benefits of exercise, its long-term effect on pain in this population is modest. A mechanistic model shows that weight loss combined with exercise affects both the biomechanical and inflammatory disease pathways and can reduce pain by 50 percent over time. However, weight regain continues to be a problem and is an important topic for further research.

***A Novel Pharmacologic Approach to Restoring Whole Joint Health*:** A large proportion of joint pain is muscle related. As an example, shoulder pain is extremely common after stroke and occurs in 30 to 70 percent of patients. This pain is thought to be caused primarily by damage to the myofascial tissues around the shoulder joint; however, imaging studies show that the degree of structural damage to the muscles does not correlate with the degree of pain. The accumulation of hyaluronic acid (HA) in muscle and its fascia can cause myofascial dysfunction; this occurrence may contribute to myofascial pain, leading to development of stiff areas and taut bands, dysfunctional gliding of deep fascia and muscle layers, reduced range of motion, and pain. A novel pharmacologic approach is using the enzyme hyaluronidase to target the excessive accumulation of HA in the extracellular matrix, increasing pain-free movement and decreasing muscle stiffness, potentially preserving and restoring whole joint health.

Comments and Discussion

- Multiple peripheral and central targets exist in joint pain and these vary across joints and individuals. Multimodal treatment approaches, to include manual therapy, physical therapy, dry

needling injections, TENS, and platelet-rich plasma therapy, are effective in treating unresolved joint pain.

- The introduction of the biopsychosocial or whole person model in research and practice more than 30 years ago has not helped to address increasing rates of disability, adherence to clinical guidelines, or the increased use and possible overuse of diagnostic imaging and biological monotherapies, which have limited effectiveness. The question, therefore, is whether it is the model itself that fails to deliver, or whether the scientific and health care communities have failed to adopt the model. For example, the American College of Physicians guidelines for low-back pain recommend nonpharmacologic treatment approaches prior to other treatments and specifically prescription medications.
- Exercise trials have not always accounted for the various sources of pain or the origin of the development of OA. Scientifically rigorous study designs that group individuals by pain or pathology type, include appropriate controls, and assess responders versus nonresponders could lead to more targeted interventions. In addition, identifying aspects of the control group and systematically defining and monitoring their "usual care" is a challenge.
- There is some evidence that an attention control arm in exercise trials does better than an arm not receiving attention.
- Implementation and adaptive trial designs are needed to identify which intervention, when, and at what dose. Exercise trials need better dosing methods. Trials need to be large enough to conduct response analyses.
- The field should design biological and mechanistic analyses of exercise interventions to understand why and how an intervention works.
- Weight loss is the primary driver of pain reduction through both biomechanical and inflammatory pathways. Decreased calories leads to decreased adipose tissue and resulting load. Decreased adipose tissue also leads to decreased inflammatory cytokines.
- The efficacy of a given intervention likely depends on the type of pain. Multimodal approaches are more generalized and work across multiple targets.
- Early data on the use of new weight loss drugs show they are affecting both the inflammatory and biochemical pathways. More study is needed in patients with joint disease to assess cost effectiveness and durability of weight loss when compared to diet and exercise.

Emerging Technologies and Models

Four presentations provided current research findings on emerging diagnostic and analytical tools to assess the presence and progression of joint pathology and pain.

***Quantitative MRI To Characterize Joint Diseases*:** Quantitative MRI (qMRI) data can be used to reconstruct quantitative maps of physical parameters, for example, relaxation times, to assess underlying biological and biochemical changes in tissue. However, these data do not produce clinical images to evaluate morphology. To fill this gap, various magnetic resonance (MR) parameters are being studied to detect early premorphological changes in the biochemical components of the articular cartilage, specifically, proteoglycans, water, and collagen. Deep learning and new MRI techniques are enabling improved clinical translation of qMRI for the characterization of joint diseases. For example, MR fingerprinting enables rapid and reliable acquisition of multiple, complementary qMR parameters

that reflect the biochemical composition of cartilage. These advances facilitate clinical translation of quantitative compositional MRI data, enabling the staging of early cartilage changes for better and more targeted patient care.

***Data-Driven Learned Quantitative MRI Biomarkers and Chronic Pain*:** The perceived association between OA imaging biomarkers and chronic pain is unclear. Deep learning models can elucidate associations between bone shape, cartilage thickness, and T2 relaxation times extracted from images of chronic knee pain to enable chronic pain prediction. These analytical tools model the complex interactions between morphological, biochemical, and biomechanical aspects of the knee joint over time.

***Methodology and Analysis of Dynamic Carpal Bone Measures Derived from 4D-MRI*:** MRI and computerized tomography (CT) arthrography can assess carpal ligament damage; however, the functional impact of such damage remains elusive. MRI technology (4D-MRI) has been developed for dynamic profiling of carpal bones with the goal to curate dynamic carpal bone metrics to improve diagnostic specificity. Quantitative studies in flexion and extension of the carpal bone produced dynamic data elements that were constructed to characterize healthy and diseased bone. The results of preliminary analyses suggest that the derived data elements have promising capabilities for characterizing carpal pathology and abnormalities.

***MR Elastography-Based Slip Interface Imaging (SII) To Assess Mobility of the Myofascial Interface*:** Myofascial pain syndrome (MPS) is characterized by pain originating from muscles and surrounding fascial interfaces. Recent efforts to understand its pathology have focused on myofascial connective tissue and the function of fascial plane mobility. MR Elastography-Based SII (MRE/SII) presents a unique, noninvasive methodology for evaluating this fascial plane mobility. Early findings provide a foundation for future research into using MRE/SII to distinguish healthy fascial planes from those that are dysfunctional in MPS patients.

Comments and Discussion

- Most imaging methodologies are acquired in a static and oftentimes unloaded configuration. More can be done to assess function with imaging, for example, how tissue properties change under load, using other modalities.
- In the past, research on joint disease focused on cartilage and then turned elsewhere over time. The presentations in this session suggest an opportunity to return to studying cartilage in addition to other tissues, potentially combined with molecular information, to understand inflammation and bone remodeling.
- Abundant clinical and scientific evidence demonstrates that imaging of structure does not correlate particularly well with pain, highlighting the need for better markers to differentiate types of pain.
- The signs and symptoms of TMJ OA include pain, a continuous inflammatory process with articular cartilage degradation, bone changes, and synovial proliferation. This joint is more susceptible to bone changes than the larger joints. As such it serves as a good model to study

bone changes using integrative predictive models combining imaging, biological, and clinical markers of this disease.

- A challenge for biomarker discovery in chronic pain is differentiating normal adaptation to injury, aging, and other factors versus maladaptation at the level of the whole joint, or even whole human. Biomarkers only offer a snapshot of the complex transition to chronic pain. Multiscale computational models are needed to interpret multimodal biomarkers.
- Promising imaging and analytical methods have to be clinically implementable and practical, necessitating collaboration between clinicians (surgeons) and diagnostic and therapeutic researchers and developers. Although the technical problems with imaging are being solved, these tools and approaches need to be actionable, less time consuming, and not likely to overload clinicians.
- To improve clinical implementation of imaging data, research should focus on a specific question that is broadly applicable. In addition, more careful crafting of trial inclusion criteria will lead to studies with findings that facilitate more targeted treatments.
- The role for qMRI to identify which patients will benefit will expand once there are treatments. Better phenotyping through such imaging will assist in triage. In the near term, scanning is not likely to find the source of pain but is useful in eliminating possibilities.
- Availability of subject-specific models is in the future, but that first requires a stepwise approach to developing objective ground truths that can be put on a scale and combined with imaging (e.g., gold-standard clinical assessments). There is some skepticism about whether this is feasible in the clinical setting. Current models are static and do not reflect movement, limiting their utility. Nonetheless, advances in imaging analysis such as automated segmentation and deep learning could incorporate dynamic imaging to enhance musculoskeletal modeling.
- Although bench validation approaches have been informative in the past, developing ex vivo tests to correlate with parameters developed in vitro is difficult and becomes even more complex in vivo.
- Since qMRI is available clinically, morphological imaging that includes segmentation and registration is crucial for generalizable and openly available patient-specific models. MRI acquisition coverage is critical. Computational strategies can be used to optimize acquisition and validation. Notably, the U.S. Food and Drug Administration (FDA) will require design controls and appropriate validation strategies to show efficacy.
- Although bone marrow lesions' association with pain has not been evaluated in imaging studies, changes in bone and inflammation are strong predictors of the presence and prediction of pain.

Challenges and Future Opportunities: General Discussion

Helene M. Langevin, M.D., director of NCCIH, chair, and Gayle Lester, Ph.D., director of extramural research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, co-chair, offered the following thoughts and observations about the 2-day workshop.

Dr. Langevin first focused on topics that were frequently discussed over the 2 days and said she appreciated the embrace of the concept of whole joint health. Discussion of mechanisms like intertissue communication highlights the multiple roles of adipose tissue and obesity in joint pain, inflammation and resolution mediators, bone, and cellular senescence. Extracellular matrix composition and tissue mechanics were described in terms of the roles of matrix synthesis and degradation, matrix fragments,

and hyaluronic acid aggregation. These factors contribute to tissue stiffness or laxity, tissue adherence, and joint mechanics. Understanding the mechanics of healthy versus unhealthy loads requires improved in vivo dynamic measurement methods. Speakers emphasized the need to integrate molecular and structural imaging and the challenge of data integration across many different data types.
The clinical aspects of whole joint health stress the importance of a whole person, biopsychosocial approach and use of multimodal therapies, such as diet and exercise or passive and active mechanical therapies. Moreover, analgesia and restoration of joint health can go hand in hand, for example, use of TENS to reduce pain during exercise. However, there are challenges in implementing what we already know. Further, it is likely that many failed clinical trials do not succeed because they do not evaluate the whole joint. This raises the question of whether robust multiscale models of whole joints are feasible and applicable to patient care.

Dr. Langevin discussed possible gaps in either what we know or what was discussed in the workshop. There was a lot of discussion about pain and the difficulty of describing it, defining it objectively, and identifying its sources. To better understand pain in the whole joint, more research on function and other aspects of whole joint health such as mobility or proprioception is needed. Personalized signatures of joint health that can be followed over time within each individual can be used to track their journey moving toward or away from health. Subject-specific modeling is ideal but complex. There was little discussion of prevention with the exception of using qMRI to detect early reversible cartilage lesions and diet and exercise to prevent OA. Although MRI techniques are improving, they focus on cartilage and bone. Soft tissue imaging is lagging behind. Finally, longitudinal studies are needed to understand the natural history of joint health, both adaptative and maladaptive phenotypes, and their evolution.

Dr. Lester made the following observations, starting with the foundation that a holistic approach to OA is essential because it is not a single disease and has varied manifestations and causations. As such, surgical, manual, and pharmaceutical interventions are needed. Treatment trials need to be more carefully designed and, to date, nonhuman models of joint pathologies have been mixed or inadequate. Workshop discussions reflected limited consensus on outcome measures other than pain.
More specifically, Dr. Lester noted the following topics: the role of stiffness in myofascial abnormalities in loss of function and instability; the actions of inflammatory cytokines and crosstalk among cell populations in the joint; the use of machine learning and AI to provide insights into the early changes and markers for the development of OA; and the need for harmonization of data sets.

Open discussion and comments centered on several overarching issues and recommendations:

- Overcome reductionist approaches to care and research through advanced study designs to evaluate multimodal interventions, such as cluster randomized designs, implementation studies, adaptive designs, and single-person precision trials.
- Seek more comprehensive understanding of function, biomechanical, and physiological factors that reflect the human condition by using appropriate mouse models that account for age, sex, and progress over time. Large animal studies are needed to approximate the size and mechanics of the human. Chips can provide a tool to develop basic understanding of the interplay among various tissues in different various mechanical environments, including profiling the molecular signatures of the joint tissues and possibly the dorsal root ganglion.
- Develop a prevention model that annually involves a physical therapy assessment using objective measures before symptoms appear.

- Weight regain after diet and exercise interventions suggests that pharmacologic approaches might be more effective. However, the benefit of being in an attention control group demonstrates the value of a psychological intervention, such as health coaching, as an investment toward better long-term outcomes at lower cost.
- Although this workshop did not focus on nontraditional approaches to joint health (e.g., tai chi, yoga, supplements, nutrition), there is a need to understand the physiological, neural, structural, and mechanical benefits or lack thereof of strategies that are widely used in the general population.
- The issue of interindividual response heterogeneity in terms of not just treatment but also disease progression can reveal much about joint health and associated pain. Studies need to answer the primary research question, but then as a secondary aim, address the wide variance around the mean. This requires large data sets.
- Epigenetic changes that can affect obesity and OA deserve more attention to deprogram and remove immune dysfunction in some individuals over generations.
- Going forward, crosstalk and crosswalks are needed across disciplines to reconceptualize and strategize around the concept of the joint as an organ in a joint system that affects many aspects of overall health.
- Patients and the public can make significant contributions to advancing the science and care, not just through enrolling in clinical trials, but also through community engagement, outreach, education, and advocacy.

The chair and co-chair thanked participants for the robust discussion. Dr. Alex Tuttle, NCCIH, closed the meeting by thanking the NIH representatives, speakers, panelists, the planning committee, the virtual audience, and those involved in logistics and communications. Ms. Catherine Law, NCCIH, moderator, thanked all participants and brought the meeting to a close.