Understanding and Restoring Whole Joint Health in Pain Management: An NIH HEAL Initiative Workshop
July 25–26, 2023; Virtual
Executive 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. The concept of whole joint health recognizes that opportunities for prevention and restoration of whole joint health and reduction in joint pain likely lie in the nutritional, psychological, and physical domains.

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 disease, 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.

Session 1 - 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. For example, the structural changes of osteoarthritis (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. 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. In the future, it may be possible to quantitatively connect structure and function to pain signals through multiscale computational models. However, the underlying pathologies leading to joint pain cannot be readily determined from radiography alone, requiring consideration of other factors. Both systemic and biomechanical risk factors can contribute to joint disease, including joint shape and alignment, injury status, and body weight. Imaging modalities such as magnetic resonance imaging (MRI) have shown that various structural alterations such as meniscal tears, subchondral bone marrow lesions (BMLs), subarticular bone attrition, synovitis, and effusion are related to knee pain. BMLs are histopathologically complex and may be a biomarker for the actual cause of pain, which is not yet fully understood. Linking phenotypes to genotypic markers may help predict individual susceptibility to joint diseases, surgical outcomes, and individual differences in responses to pain treatments. In sum, joint pain is a complex mix, and both structure and pain should be treated. Many factors, including increased innervation due to inflammation, reprogramming of synapses, and epigenetic and cognitive changes, can play roles in maintaining long-term pain. Understanding root mechanisms of these different types of OA pain needs to be more carefully considered in preclinical models as well as ongoing clinical trials. Researchers are encouraged to look to causal factors beyond cartilage restoration or repair to address joint pain.

Session 2 - Mechanisms of Whole Joint Pathology

Four presenters discussed several mechanisms that contribute to "whole joint" pathology. Muscle has long been considered the quantal element in the control of movement. However, recent research has demonstrated strong interactions between muscle fibers and intramuscular connective tissue as well as between muscle fibers and fasciae, suggesting that muscle can no longer be considered the only element that organizes movement. Collectively, these interconnected tissues are referred to as the "myofascial unit." Incomplete understanding of the nociceptive innervation of the joint and all of its components hinders development of novel, effective pain therapies and interventions. Recent research has shown that joint innervation is not static, and research is needed to document the precise anatomy of innervation changes that occur in response to joint degradation. Obesity-induced OA involves both metabolic and biomechanical factors, and a key link is excess adipose tissue. Adipose tissue is necessary for the normal development of muscle mass and strength, and leptin is the key adipokine mediating this regulation. Cartilage injury may induce changes in adipose tissue found external to the knee joint, showing a bidirectional crosstalk mechanism that can be harnessed for therapeutic development. In addition, the intra-articular space is a unique environment where direct tissue-to-tissue contact and exchange of soluble messengers maintain joint homeostasis and generate a whole joint response to injury or disease. Future pain interventions could take advantage of shared tissue mechanisms or messengers, including nerve-tissue communication. Such communication is most evident by the involvement of all joint tissues in response to a primary insult to a single tissue such as cartilage, meniscus, tendons, or ligaments. Mediators of such communication that promote spreading and chronicity of pathogenic signaling across all joint tissues are potentially promising therapeutic targets. A critical component in understanding the complexity of OA pain will involve implementing statistical and computational approaches to analyze large and diverse high-dimensional data sets of subjects over the lifespan to understand intra- and interindividual changes and differences.

Session 3 - Differences Among Joint Types and Joint Pain Populations

Heritable disorders of connective tissues serve as models for joint disease. 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. 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. Painful conditions in cervical spinal facet joints and the temporomandibular joint also provide useful models to elucidate the mechanical and molecular mechanisms contributing to synovial joint pain. Better models are needed to assess joint mechanics in different pain conditions, taking into account sex differences and different age groups. For example, structural damage and joint instability vary across disorders, with hypermobility disorders particularly prone to joint structure damage. Disparities in joint pain exist; groups historically underrepresented in medical research and care bear a higher burden of many chronic medical conditions, including OA. For example, Black patients with symptomatic knee OA have poorer function, most of which is explained by differences in socioeconomic status and physical health. Understanding the similarities and difference in pathology, pathophysiology, pain manifestations, and mechanisms among joints will yield better whole joint treatments and interventions.

Session 4 - Interventions To Address Joint Pain and Disease

Transcutaneous electrical nerve stimulation (TENS) can serve as a nonpharmacologic treatment for pain. Recent research has provided evidence that TENS reduces movement pain and fatigue and is a safe and cost-effective intervention. 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, the use of manual therapies for pain management in OA is low compared to the use of pharmacologic therapies. Work is needed to implement established nonpharmacologic therapies to treat joint pain. For example, only 10 to 15 percent of patients who completed a total knee arthroplasty procedure elected to have physical therapy prior to surgery. More research is needed to understand how exercise-based therapies can reduce joint pain. Obesity is positively associated with joint pain wherein greater degrees of obesity correlate with increased joint pain. Exercise reduces joint pain in people with obesity and/or knee OA; however, the effect size decreases over time, and there is evidence that attention control groups do better than those receiving no intervention. Multiple tissues can contribute to joint pain, and pain relief may depend on one or more interventions that target multiple tissues. For example, the accumulation of hyaluronic acid (HA) in muscle and its fascia can cause myofascial dysfunction, and this may be a mechanism related 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 or restoring whole joint health. Multiple peripheral and central targets exist in joint pain and these vary across joints and individuals. Multimodal treatment approaches could help resolve chronic joint pain. Potential combination therapies discussed included manual therapy, physical therapy, dry needling or injections, TENS, and platelet-rich plasma therapy.

Session 5 - Emerging Technologies and Models

Quantitative MRI (qMRI) data can be used to reconstruct quantitative maps of physical parameters (e.g., relaxation times) to assess underlying biological and biochemical changes in tissue. Various magnetic resonance (MR) parameters are being studied to detect early premorphological changes in the biochemical components of the articular cartilage, including proteoglycans, water, and collagen. Deep learning and novel MRI techniques (e.g., MRI fingerprinting) can enable improved clinical translation of qMRI for joint disease characterization. Novel technologies developed to aid in joint modeling and analysis can also improve the perceived association between OA imaging biomarkers and chronic pain. For example, new models developed using deep learning artificial intelligence technologies can elucidate associations between bone shape, cartilage thickness, and T2 relaxation times extracted from images of chronic knee pain that allow researchers to begin to predict pain onset using noninvasive assessments. In the area of kinetic imaging and analysis, 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. Myofascial pain syndrome (MPS) is characterized by pain originating from muscles and/or 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 plane mobility and could be used to distinguish healthy fascial planes from those that are dysfunctional in MPS patients. Abundant clinical and scientific evidence demonstrates that currently available imaging measurements of structure do not correlate particularly well with pain, highlighting the need for better markers to differentiate types of pain. High-quality preprocessing, including the use of gold-standard clinical assessments, is needed to ensure data conformity and high-quality datasets. Future imaging studies could incorporate dynamic imaging to

capture changes in joint characteristics over time. Finally, in order for promising imaging and analytical methods to be clinically implementable and practical, collaboration between clinicians (surgeons) and diagnostic and therapeutic researchers and developers will be critical. Although the technical problems with imaging are being solved, these tools and approaches need to be actionable, less time consuming, and efficient, as not to overload clinicians.

General Discussion - Challenges and Future Opportunities

Discussion of mechanisms, such as intertissue communication, highlights the importance of understanding contributions across multiple tissues involved in the "whole joint." Of particular relevance to this topic are the multiple roles that adipose tissue, bone, and cellular senescence play in progressing joint degeneration and joint pain; as well, the contributions of obesity, age, and tissue inflammation (and/or resolution) are important mediators. 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. However, there are ongoing challenges in implementing therapeutic strategies that have already demonstrated efficacy, including physical therapy and exercise-based therapies. More broadly, it is likely that many failed clinical trials do not succeed because they do not evaluate the whole joint. 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. There was little discussion of early diagnostic and prevention strategies, with the exception of using qMRI to detect early reversible cartilage lesions and diet and exercise to prevent OA. Longitudinal studies are needed to understand the natural history of joint health, both adaptative and maladaptive phenotypes, and their evolution. A holistic approach to treating joint pain is essential because joint pain is not the result of a single disease and has varied manifestations and causations. As a result, multiple interventions may be needed to effectively treat joint pain, including the use of nonpharmacologic interventions, pharmaceutical therapies, and surgery. Treatment trials need to be more carefully designed and, to date, preclinical disease models are insufficient to understand the complexity of joint pathology. The field can 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. 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.