

Preface

Pain in Rheumatic Diseases



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Editor

The 5 classic signs of inflammation include redness (Latin *rubor*), pain (*dolor*), heat (*calor*), swelling (*tumor*), and loss of function. Hence, it is not surprising that pain would be a frequent concern of patients with rheumatic diseases. The mechanisms associated with pain perception are complex and involve both central and peripheral processes associated with nociception coupled with responses to individualized experiences, such as sleep disturbances, psychosocial stresses, and past circumstances. Although there have been exciting advances in the treatments of inflammation with an increasing number of targeted therapies, it has become clear that the clinical resolution of redness, warmth, and swelling may not be accompanied by complete relief of pain. Recent advances in imaging technology, clinical assessment tools, and animal models are providing new insights into this issue.

In this issue, important clinical and mechanistic questions are addressed across major areas that affect patients with rheumatic diseases. In the introductory article by Minhas and Clauw, current concepts of pain mechanisms are reviewed. The authors note that patients often have mixed pain states, and Minhas and Clauw provide a basic framework for clinicians to deconvolute components of nociceptive pain (due to tissue damage or inflammation), neuropathic pain (associated with nerve damage and dysfunction), and nociplastic pain (central sensitization). This last component of pain is least likely to respond to medications that treat inflammation or nociceptive pain and presents interesting challenges. These principles apply to adolescents as well geriatric patients. Borenstein and Balagué discuss recent data regarding spinal pain, the most common form of musculoskeletal pain, with an emphasis on younger and older populations. Symptoms of back pain are increasing among adolescents, and the older population is at risk for developing spinal stenosis. Diagnostic strategies and short- and long-term treatment outcomes are presented.

Given the complexities of pain, *in vitro* experimental approaches have been limited in developing our understanding of the intercellular signaling networks, and animal

models have provided additional insights. Dos Santos and colleagues outline studies that concurrently assess the painlike behaviors in male and female rodents in inflammatory arthritis models. There are clear mechanistic differences between the sexes that are only partially explained by sex hormones and their receptors. Malfait and colleagues review specific changes in the peripheral neuronal pathways underlying joint pain in osteoarthritis. They provide perspectives on the plasticity of the nociceptive system in osteoarthritis, and the associated changes in the structural, physiologic, and genetic properties of neurons in related pain pathways. The authors posit that the changes in neurons that interact with the innate immune system and innervate degenerative joints may lead to the identification of additional treatment targets for osteoarthritis and other pathologic conditions that manifest as arthralgias.

Beyond the categorization of global pain states, specific diseases can also contribute to our overall understanding. Three articles summarize the current knowledge base in relation to pain for systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis. Pisetsky and colleagues discuss the mechanisms of pain arising in lupus and describe the advantages of categorizing symptoms as 2 types of manifestations of pain in the context of other symptoms, including fatigue and depression. This approach may be useful in addressing complex symptoms in a patient-centered manner. Iyer and Lee outline the mechanisms that lead to central pain sensitization in rheumatoid arthritis and the perpetuation of pain with minimal or no nociceptive stimulation. Quantitative sensory testing and neuroimaging methods to study different components of pain in rheumatoid arthritis and their use in assessing therapeutics are also discussed. The interaction of immune cells and neurons also plays a role in the development and perpetuation of pain perception in ankylosing spondylitis. Pathon and Inman present how advanced imaging techniques have been used to investigate the interplay of various brain networks in the perception of pain. These networks exhibit functional connectivity, which modulates pain perception in ankylosing spondylitis. Imaging and other studies that demonstrate sexual dimorphism in pain perceptions are also discussed.

In the United States, there has been mounting concern surrounding the long-term use of opioids for chronic pain. Clearly new treatment strategies are needed, particularly for nociplastic pain. Three articles examine different facets of potential treatment strategies. Dietz and colleagues focus on the benefits and risks of targeted therapies that block nerve growth factor, a neurotrophin that mediates pain in a variety of pathologic conditions, including cancer and osteoarthritis. The promising data from recent clinical trials demonstrating long-term pain relief are presented, and the caveats of safety signals for rapidly progressive osteoarthritis and enhanced risk with concurrent use of nonsteroidal anti-inflammatory drugs are discussed. Although cannabinoids are not necessarily a new therapeutic class, Hulland and Oswald present the utility of cannabinoids in treating painful conditions following recent changes in the medicolegal landscape. This article outlines the need for high-quality data to guide clinicians in the use of this therapy. It would be remiss to assume that all therapeutic strategies exclusively involve injections and tablets. Martin and colleagues provide an overview of nonpharmacologic options for the treatment of pain in patients with inflammatory arthritis, such as psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. These authors explore the evidence that supports specific modalities of nonpharmacologic pain control, such as mindfulness, cognitive behavioral therapy, exercise, massage, splinting, and heat therapy. They seek to provide the practitioner with a framework for pain control that addresses factors that influence the experience of pain.

Clinical and basic science research has advanced our understanding of the complexities of different pain states. Clearly, as diagnostic, imaging, and molecular tools continue to improve, new opportunities for clinical insights and applications are emerging. Here, I invite the readers on behalf of the authors to use these articles to incorporate a new understanding of the complexities of pain experienced by patients and enhance our treatment approaches with a new eye toward what is likely the most compelling issue for our patients.

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