

Editorial

Inflammatory and Noninflammatory Disease Activity in Rheumatoid Arthritis: The Effect of Pain on Personalized Medicine



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Disease activity in rheumatoid arthritis (RA) is often described in terms of inflammation, although noninflammatory mechanisms are also integral to the disease. Pain is the most important symptom for many people with RA,¹ and is therefore a key component of clinically relevant measures of RA disease activity. As an example, the Disease Activity Score in 28 joints (DAS28) incorporates a visual analog scale for general health (VAS-GH) and tender joint counts (TJCs), which are largely dependent on pain. Inflammation contributes to RA pain, but so also do noninflammatory mechanisms. In this edition of *The Journal of Rheumatology*, Wohlfahrt et al² use DAS28 to define disease activity, explicitly incorporating both inflammation and non-inflammatory pain into their concept of active disease.

Noninflammatory pain mechanisms are multiple and complex, and pain can be experienced in different ways by different people and at different times. Pain may be constant or intermittent, localized or widespread, and may be described by a variety of words, such as throbbing, burning, gnawing, or

shooting. Pain is often reduced during measurement to a single number, for example, in answer to the global question, “How severe has your pain been over the past week?”³ However, the various pain characteristics are mediated by different mechanisms within peripheral and central nervous systems. Quantitative sensory testing (QST) can be used to explore aspects of hypersensitivity that contribute to the experience of pain.

QST has used multiple modalities with standardized stimuli to explore different pain mechanisms. Pain hypersensitivity may indicate either increased facilitation or decreased inhibition of nociceptive transmission. Pressure pain thresholds (PPTs) measure the lowest pressure experienced as pain when a standardized pressure is applied, for example, to a joint or muscle. PPTs are reduced if there is sensitization of peripheral nociceptive neurons (eg, due to inflammation), but they also are modulated by central pain processing. PPTs therefore might be reduced not only at the site of inflammation but also at more distant sites. Conditioned pain modulation (CPM) measures the change in pain detection threshold that results from application of a second (conditioning) painful stimulus at a distant site. CPM can indicate activity in endogenous analgesic pathways within the brain and spinal cord, and less efficient CPM is associated with greater sensitivity and more severe pain.

Combining multiple QST indices of central pain processing, in an attempt to generate a single, simple model of central pain hypersensitivity, belies its heterogenous nature. Wohlfahrt et al² present data from the Central Pain in RA (CPIRA) cohort study,⁴ supporting that different pain mechanisms could drive DAS28 in different ways in different patient subgroups.² They found that low PPT (greater sensitivity) at the knee predicted higher DAS28 scores after disease-modifying antirheumatic drug (DMARD) treatment in people with low or moderate disease activity, whereas less efficient CPM predicted higher posttreatment DAS28 scores in those with high baseline disease activity.² Why do these QST indices predict DAS28 scores, and what might lead to differences between mechanistic pain subgroups?

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Sensitization, as indicated by low PPT or CPM, may directly drive pain and be a barrier to pain improvement. QST evidence of sensitization could also indicate a subgroup of people who, for reasons other than sensitization, are more likely to have poor DAS28 outcomes. QST sensitization indices may be associated with female sex, obesity, or pain experienced over a long period of time. People with QST evidence of sensitization are more likely to have comorbidities, particularly other conditions such as fibromyalgia that are associated with mood or sleep disturbance, fatigue, or pain at multiple sites. They may be more likely to be using opioid analgesics and display catastrophic thinking. Each of these factors might predict pain other than through effects of sensitization, and some, such as obesity, could predict inflammation over and above any effects on pain.⁵

Lower PPT and CPM are frequently observed in those with more severe pain, and pain itself might drive prognosis or treatment responses through mechanisms other than sensitization. For example, pain can be demotivating, drive a quest for rapid but short-term solutions such as glucocorticoids in preference to slow acting disease-modifying agents, and be a barrier to engagement in rehabilitation. PPT and CPM are therefore indices of sensitization, but lack specificity, and the associations observed by Wohlfahrt et al² may be explained by confounding factors rather than sensitization itself. Further, it is unknown at present whether all factors associated with PPT are also associated with CPM, or vice versa, and some of the apparent differences in DAS28 prediction between PPT and CPM could be caused by modality-specific confounding factors.

QST evidence of sensitization is more pronounced in people with severe or longer-established pain, but the temporal development of different sensitization mechanisms in RA is incompletely understood. It is unknown whether increasing time from pain onset might be characterized by a shift from mechanisms underlying PPT to deficient endogenous central analgesic mechanisms. Further, the data of Wohlfahrt et al² intriguingly suggest that different DAS28 categories are associated with evidence of pain sensitization from different QST modalities, raising the possibility that different inflammation phenotypes in RA can drive different pain mechanisms. Better understanding how inflammation causes or predicts pain in different people should lead to better targeting of specific antiinflammatory interventions to best improve pain outcomes in the future. Taking this idea a step further, people with different DAS28 scores are likely to receive different disease-modifying treatment. People with low or moderate DAS28 scores may be treated with methotrexate as monotherapy, whereas those with high DAS28 scores are more likely to receive glucocorticoids and biologic therapies. It is possible that these different interventions affect sensitization mechanisms differently, and these different therapeutic effects might, in part, affect the predictive value of PPT and CPM. If so, then matching PPT and CPM phenotypes to DMARDs, and clinical phenotyping combining DAS28 and QST could enhance clinical benefit, including both inflammation and pain, that can be achieved from existing therapies.

Current assessment tools should be mechanistically interpreted only with caution. DAS28, although labeled as an index

of inflammatory disease activity, might also be an index of pain severity and of central sensitization. Indeed, DAS28 components differ in their specificity for inflammation, with acute-phase reactants and swollen joint counts being less influenced by pain and sensitization than are TJC_s and VAS-GH.⁶ Further, PPT and CPM not only are labeled as indices of sensitization, either peripheral or central, but are also influenced by contextual factors, including interaction between the assessor and participant. Measured values might be different if a male participant is assessed by a female rather than by a male healthcare practitioner or researcher. PPT values distant from a site of joint inflammation can indicate central sensitization⁷ but may instead reflect systemic or genetic factors that affect peripheral nociceptor sensitivity across all body sites. This limitation is particularly relevant in RA, where circulating autoantibodies have been incriminated in causing widespread peripheral sensitization.⁸ Conditioning stimuli used in CPM may activate endogenous analgesic pathways, but these could also be distracting, diverting attention from pain, rather than necessarily reducing pain perception. Further interventional and mechanistic studies are needed to be confident of the mechanisms by which different QST modalities might predict DAS28 outcomes in different people.

The findings of Wohlfahrt et al have several important implications for future research. They present data on just 2 indices of sensitization (PPT and CPM). Other indices exist. Temporal summation measures changing pain sensitivity with repeated application of a nociceptive stimulus and has been related to the spinal neurophysiological phenomenon of “wind up.”⁹ Offset analgesia measures “a disproportionately large pain decrease after a minor noxious stimulus intensity reduction.”¹⁰ Even in people without arthritis, different body sites (eg, forearm, knee), and tissues (eg, skin, muscle, periosteum) can display different pain sensitivities, perhaps due to different tissue biomechanics, innervations, or central nervous system connections. Further research is needed to refine and validate QST modalities that might best home in on the precise pain mechanisms that are most relevant to predicting disease activity or pain in different patient groups. The analysis by Wohlfahrt et al² is exploratory, and their hypothesis that indices of discrete pain mechanisms differentially predict outcomes in subgroups of people with RA merits prospective testing.

The longitudinal Frederiksberg hospital’s Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME-cohort) study previously indicated that temporal summation and painDETECT questionnaire were not significant longitudinal predictors of DAS28, despite encouraging cross-sectional findings.¹¹⁻¹³ The findings of Wohlfahrt et al² point now to other tools with which to test causal relationships between pain, inflammatory disease activity, and sensitization. PPT and CPM are laboratory tests that require careful standardization. Recent efforts to develop simpler protocols and equipment for “bedside QST”¹⁴ will need to be progressed if their potential to inform treatment and treatment outcomes is to be translated to the clinic. Further research is needed to determine whether specific DMARD or targeted immunosuppressive therapies reduce components of sensitization, and whether indices of sensitization

can help determine who will most benefit from which treatment. Deeper characterization and new findings about inflammatory disease activity may also help reveal how inflammation itself can modulate and be modulated by pain sensitization and its treatment.

Discrete prognostic or predictive factors may further inform the design of efficacy randomized controlled trials (RCTs). Recruitment criteria might consider sensitization indices that predict outcomes to increase study power and reduce drug development costs. Should people with evidence of central sensitization be included or excluded from RCTs, and should indices of sensitization inform stratification within trials? Wohlfahrt's coauthors are among the few to have published a pilot trial of stratification according to sensitization, informing possible criteria that could be used in future trials.¹⁵ Restricted inclusion criteria might increase trial sensitivity but might also reduce generalizability to typical patient populations. Many RA trials restrict eligibility to those with active inflammation, for example, by excluding people with fewer than 4 swollen joints, but usually remain agnostic about noninflammatory pain mechanisms. This recruits a trial population with active RA who may be more liable to have DAS28 response to some immunomodulatory treatments but may conceal treatments that could reduce disease activity through noninflammatory mechanisms. Will stratification based on indices of pain sensitization identify different treatments that will be effective at improving pain or DAS28? It has been proposed that Janus kinase and signal transducer and activator of transcription (JAK-STAT) inhibitors have an effect on RA pain above that expected by its immunosuppressive actions, possibly by directly interfering with sensitization pathways.^{16,17} Are there other DMARDs that are more likely to improve pain and noninflammatory disease activity in people with high or low levels of sensitization? Reciprocally, will mechanism-specific pain management improve disease activity in RA?

To conclude, RA disease activity is a complex of inflammatory and noninflammatory mechanisms. Inflammation and pain are closely integrated, and both result from multiple diverse mechanisms. DAS28 is an index of both inflammation and pain and is a useful tool with which to stratify for treatment and evaluate outcomes. Different targeted treatments might address different components of the inflammatory and pain pathways. More specific tools would help to decide which treatments are most likely to benefit which patients, and subsequently, whether they have achieved the outcome that should be expected from that treatment. Together, indices of sensitization and of specific immunologic mechanisms may best enable personalized medicine to reduce disease activity in people with RA.

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