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Fibromyalgia and Centralized Pain in the Rheumatoid Arthritis Patient

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Abstract

Purpose of review—Individuals with rheumatoid arthritis (RA) have traditionally been characterized as having nociceptive pain, leading to the assumption that effective immunosuppression should be enough to provide effective pain management. However, despite therapeutic advancements providing excellent control of inflammation, patients continue to have significant pain and fatigue. The presence of concurrent fibromyalgia (FM), driven by augmented central nervous system processing, and largely unresponsive to peripheral therapies, may contribute to this pain persistence. This review provides updates in fibromyalgia (FM) and RA as relevant for the clinician.

Recent findings—Patients with RA have high levels of concomitant FM and nociplastic pain. The presence of FM can lead to higher scores on disease measures erroneously indicating that worse disease is present leading to the increased use of immunosuppressives and opioids. Disease scores that provide a comparison between patient-reported and provider- and clinical factors may be helpful to indicate centralized pain. Interleukin-6 (IL-6) and Janus kinase (JAK) inhibitors, in addition to targeting peripheral inflammation, may provide pain relief by acting on peripheral and central pain pathways.

Summary—Central pain mechanisms may be contributing to pain in RA is common and should be distinguished from pain directly arising from peripheral inflammation.

Keywords

Rheumatoid arthritis; fibromyalgia; centralized pain; nociplastic pain

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Conflicts of Interest:

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation, pain and stiffness resulting in joint damage and disability if left untreated. Despite therapeutic advancements providing excellent control of inflammation, patients continue to have significant pain and fatigue (1). Addressing these unmet needs have been elevated to top clinical and research priorities(2). Pain in RA is often thought to be the result peripheral inflammation and nociceptive. However, multiple studies have found discordance between pain and inflammation, and concomitant fibromyalgia (FM) is increasingly being recognized as a reason why certain subgroups of patients with RA suffer from pain despite appearing to have low clinical inflammation noted(3, 4). Patients with RA frequently experience heightened sensitivity to pain in a widespread distribution, suggestive of abnormalities in peripheral and central pain processing (5).

Fibromyalgia and Nociplastic Pain

In 2016, The International Association for the Study of Pain (IASP) coined the term ‘nociplastic pain’ which is characterized by augmented central nervous system (CNS) pain and sensory processing and diminished modulation (6). Previously referred to as “central pain,” the symptom hallmarks include diffuse hyperalgesia (increased pain to normally pain stimuli) or allodynia (pain to normally non-painful stimuli). CNS-derived symptoms including fatigue, non-restorative sleep, cognitive dysfunction, memory and mood disturbance are common. (7-9)

Recent prevalence estimates of FM in RA have been from 17.7%- 29% as compared to approximately 2% in the general population (10, 11) Several other nociplastic pain syndromes have been noted which the NIH coined Chronic Overlapping Pain Conditions (COPCs)(12). In addition to FM, the 10 other conditions are characterized by hyperalgesia and allodynia, along with many CNS symptoms complaints(12).

A recent large single-center retrospective study, using ICD codes to evaluate the presence of COPCs in 5 rheumatic diseases, reported that COPCs were incredibly common amongst patients with RA, with the highest being chronic low back pain (cLBP) in 39.5%, followed by migraine, FM, chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS), in 12.9%, 10.7%, 8.9% and 7.7%, of patients respectively (13). Rates were higher among Black patients and those using public insurance. Overall patients with rheumatic diseases, those with one or more COPC were more likely to report depression and anxiety, as well as more frequent emergency department visits, surgeries, and hospitalizations (13).

Impact of FM on clinical evaluation and disease assessment:

The cornerstone of pain management in RA is guided by treat-to-target (T2T) approach aiming to for clinical remission and prevent structural damage and disability. Clinical examination is paramount, though overlapping symptoms of joint pain, stiffness, waxing and waning of symptoms can make diagnosis challenging. A recent study noted that when using central sensitization inventory (CSI) and SF-McGill pain questionnaire to assess CS in patient with RA, the main descriptors of pain according to severity of CSI scores were

"sharp" and "stabbing" whereas those of pain according to disease activity were "tender" and "throbbing" (14). CSI was noted to be associated with physician global assessment minus patient global assessment (PGA) (14).

Composite clinical and laboratory-based disease activity assessments, such as the DAS28 are commonly used to as a surrogate measure of RA activity and to drive treatment decisions and responses. By heavily weighing the tender joint count (TJC) and including PGA, the presence of FM on can artificially inflate the DAS. In fact DAS28 have been found to be higher in RA patients with FM compared to those without (15).

Following a T2T approach can potentially lead to overtreatment. The same study reported an increased use of glucocorticoids (GC) and higher rate of biologic switching due to non-response in RA patients with FM vs those without (15). Another study assessing FMNess – when using criteria such as ACR 2011 as a continuous measure rather than a discrete diagnostic cut off – found that patients with RA reporting high/very high baseline FMness were more likely to be taking glucocorticoids (GC) at follow-up compared to those with low FMness [OR 4.99 (95% CI 1.20, 20.73) (16). The association was stronger with joint pain rather than somatic symptoms, and persisted after adjustment for SWJ and C-reactive protein (CRP), suggesting persistent GC use was not merely due to high inflammatory disease activity (16).

Measures such as the discordance score (DS) and DAS28-P index which allow for comparison of the patient-reported components to provider-reported (PRF) and clinical (CF) and lab components (LF) can be useful discriminatory measure of non-inflammatory pain mechanisms in RA(17-19).

Findings from the CareRA trial reported a rapid improvement of PRF, CF and LF scores with treatment, though a subset of patients did not have the same improvement in patient-reported scores and higher DS by week 8 (18). Similarly, another study reported persistently high DAS28-P index scores in patients who were "partial responders" and "non-responders" to treatment by patient-reported measures, had higher uses of DMARDs, despite having minimal radiographic progression and low joint erosion scores over time(17). Use of these measures clinical may be useful to identify a subset of patients who have non-inflammatory pain contributing to their symptom complex and avoid unnecessary immunosuppression.

This is additionally an important consideration as adjunctive opioid use for RA pain has been increasing. In a recent study based on the National Ambulatory Medical Care Survey (NAMCS), Huang et al. reported that a fourth of all RA visits involved opioid prescriptions, and the number of opioid prescriptions more than doubled from 1.43 million prescriptions in 2011–2012 to 3.69 million in 2015–2016 (20). This is especially concerning as a recent review did not find any studies supporting its efficacy in terms of function or pain control (21). In fact, opioids were associated with increased risk of fracture, delayed and decreased DMARD use potentially delaying care and masking symptoms of active disease. They concludes that opioids do not have a routine told in the management of rheumatologic diseases (21).

DMARD and Biologic considerations:

Neuroimaging has previously provided evidence for the alleviation of pain symptoms in patients with RA treated with TNF-α inhibition, with the downregulation of nociceptive brain activity in the somatosensory cortex within 24 hours, well before changes in inflammation evidenced by joint swelling are observed around day 14 (22).

Interleukin 6 (IL-6) is a pleiotropic cytokine found to have a role in peripheral and central pain sensitization(23). Data from sarilumab randomized control trials (RCTs) and open-label extension (OLEs) assessed the prevalence of disproportionate articular pain (DP), defined by pain more severe than expected based on the amount of joint swelling and its response to sarilumab (24). A fourth of patients with RA experienced DP, which responded well to sarilumab(24) supporting the concept that other mechanisms (potentially mediated via IL-6 sensitization) in addition to inflammation contribute to pain.

Recent studies have also supported JAK inhibition having increased direct analgesic effects on peripheral and/or central sensitization. Data from RA-BEAM and RA-BEGIN trials found a superior efficacy of baricitinib with regard to more rapid improvement of pain early RA and more advanced RA as well as for other JAK-inhibitors (JAKi) in comparison to TNF blockage or IL-6 inhibition(25-27), showing that baricitinib is superior to adalimumab in alleviating pain, with a similar anti-inflammatory effect.

A recent extensive meta-analysis, demonstrating that JAKi showed a significantly greater pain-relieving effect compared to bDMARDs supported these findings(28) In addition, the CRP values indicating the intensity of the inflammatory reaction were also lower in the JAK inhibitor group(28). Additionally, a post-hoc analysis of phase 3 trials of baricitinib found pain reduction was similar between opioid users and non-users, which was not observed for adalimumab, suggesting opioids attenuate pain reduction effects(29). A recent systematic review also reported clinically meaningfully improvement in mental health outcomes over time in patients with RA taking JAKi (30).

Adjunctive management strategies:

Adjunctive treatments such as assessment by hand occupational therapy, structured exercise programs, and utilizing mobile health (mHealth) interventions combining home exercises programs and self-management recommendations have been shown to improve overall joint function, pain levels and satisfaction compared with usual care (31-33). Interestingly, a recent study evaluating custom-made foot orthoses (FO) reported that not only were there expected reductions in foot ($p < 0.001$) and leg pain ($p = 0.012$), but pain reduction was noted in the arms and hands ($p = 0.014$)(34). The authors queried if this interesting observation could indicate changes in central pain sensitization as result the intervention (34).

Fatigue, Sleep and Psychosocial Considerations:

In addition to pain, addressing the CNS- mediated somatic complaints, such as fatigue, sleep disturbances and psychosocial factors are key to optimizing QOL in patients with

RA. Fatigue is very common in patients with RA with 40% noting severe fatigue and is consistently rated as one of their top priorities (35). Different indices of disease activity, and objective markers of inflammation have only been weakly and inconsistently associated with fatigue severity (36).

Fatigue can be difficult to treat, and data from the T2T trial CareRA reported only one in four patients making lasting improvement and 20% even experiencing worsening multidimensional fatigue over time (37). When fatigue is related to disease activity early and aggressive treatment is linked with improvements in long-term fatigue and disease remission (37). However, it is important to note a subgroup of patients who report somatic complaints at baseline will not improve with peripherally directed therapies and will likely need a more holistic approach to management. The CareRA trial noted higher 5-year fatigue levels were seen in patients with more perceived disease impact (pain, PGA, poorer mental health and sleep) but lower SWJ at baseline (37). Similarly, the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) cohort identified a subgroup of patients with RA experiencing high levels of pain, fatigue, and psychosocial distress 3 years after RA diagnosis. This subgroup already displayed high levels of pain and functional disabilities at baseline without a corresponding increase in inflammatory parameters (38). Lastly, using data from an early RA inception cohort that 34% of patients reported unacceptable pain (UP) 5 years after inclusion. Predictors included lower SJC and more perceived patient-reported disease impact at baseline. Having UP and low inflammation after 5 years was negatively associated with anti-CCP antibodies (39).

Sleep disturbances are common in patients with RA and have been shown to be linked to increased pain (40, 41). Data from a recent multi-center study reported quantitative sensory testing (QST), used as a surrogate for pain sensitization, was a statistically significant mediators between sleep disturbances and patient-reported pain at 12 weeks after initiating a new DMARD (41).

Encouraging patients to be engaged in their care may be helpful to promote great patient empowerment levels, which has been associated with lower pain score and better physical function, a relationship which remained even after adjusting for SJC and markers of inflammation (42). In another cohort of patients with early RA, negative illness perception was associated with lower probability of sustained remission (SR) and of the patients who achieved remission, those with low psychosocial burden were more likely to remain in SR (43). Providing patients with resources such as Pain Guide https://painguide.com/ can be a helpful place to start.

Future Directions:

The role of the macrophage phenotype in the synovium and dorsal root ganglion, and glial cells in the CNS is still being elucidated, but given the data is suggested to be a key player in the onset and maintenance of arthritis-associated pain (44). Photoacoustic (PA) imaging, based on the use of laser-generated US, is currently being studied to detect the oxygenation status of tissue in patients with RA (45). Studies have found photoacoustic imaging–detected hypoxia has been associated with higher disease activity in participants with RA (45), and

this may be another methodology to detect true synovitis. Use of different brain metrics based on magnetic resonance (MR) imaging is also being studied as a potential biomarker of fatigue in RA (46).

Conclusion:

The mechanisms of pain in RA extend beyond peripheral inflammation, and FM as form of central sensitization is commonly co-morbid, can affect disease activity scores and result in overtreatment. Clinicians should have a high index of suspicion for FM when patients report pain, fatigue and other CNS-related complaints that are discordant to their clinical exam and laboratory data. Considerations for centrally acting mechanisms when considering biologic use, as well as incorporating adjunctive non-pharmacologic can be helpful tools when considering management of RA-related pain.

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Key Points:

Despite the prevalent use of biologics in the treatment of rheumatoid arthritis resulting in excellent control of disease, many patients continue to complain of persistent pain.

A Treat-to-Target approach for pain in RA is the cornerstone of treatment, however, may result is overinflation of disease measures erroneously indicating that higher disease activity and resulting in overtreatment.

Comparing the subjective and objective measures of disease activity scores may be helpful to distinguish central pain mechanisms separate from peripheral inflammation.

Interleukin-6 (IL-6) and Janus kinase (JAK) inhibitors, in addition to targeting peripheral inflammation, may provide pain relief by acting on peripheral and central pain pathways.