Commentary

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Pain sensitization in arthritis: cause or effect of chronic pain?

"An interesting observation in recent years has been the finding of pain sensitization in people with osteoarthritis and rheumatoid arthritis. By sensitization, we mean a heightened perception of pain sensitivity in people with arthritis, often at sites distal to the areas of joint swelling and damage."

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Pain in rheumatic disease

Arthritic diseases place a high burden on healthcare globally, causing significant pain and reduced function in those affected. With a rising world population and the increasing epidemic of obesity, the number of people with chronic arthritic diseases is set to rise. We now have a broad range of analgesic drugs of various classes available to treat patients with arthritic disease. For inflammatory arthritides, there are also a variety of treatment modalities available, including oral disease-modifying antirheumatic drugs (DMARDs) and biologic therapies. Response to DMARDs, particularly in the inflammatory disease arena, can often be accurately measured using tools such as clinical assessment of synovitis or joint effusion, systemic inflammation measured on blood testing including the erythrocyte sedimentation rate and C-reactive protein and imaging modalities including ultrasound or MRI to detect and quantify the level of synovitis, synovial hypertrophy, joint effusions and extent of joint erosions [4].

An interesting observation in recent years has been the finding of pain sensitization in people with osteoarthritis (OA) and rheumatoid arthritis (RA). By sensitization, we mean a heightened perception of pain sensitivity in people with arthritis, often at sites distal to the areas of joint swelling and damage. Sensitization may explain why people with OA and RA continue to experience pain, despite use of disease-modifying and analgesic therapies in the long term. In this commentary, we discuss the evidence for sensitization in OA and RA, with data from recent studies. We will explore the hypothesis that future treatment plans for people with chronic arthritis may need to incorporate a wider range of measures, including of pain sensitization, in order to achieve optimal disease control.

What is sensitization?

Rheumatic diseases cover a wide range of over 200 conditions, the most common of which include conditions such as RA and OA. Historically, RA has been considered an archetypal autoimmune-mediated inflammatory condition. In contrast, OA has previously largely been described as a mechanical joint disorder, with increasing age, joint damage and obesity as strong risk factors for its development. Various factors contribute to pain in both RA and OA, including inflammation mediated by release of prostaglandins [1], leukotrienes [2] , cytokines [3] and mechanical factors leading to local joint tissue destruction.

Recent observations have shown how people affected by arthritis may, however, continue to experience pain, despite use of anti-inflammatory therapies, for example, nonsteroidal anti-inflammatory drugs and TNF-α inhibitors (TNFi) [4]. Such observations have led to the hypothesis that pain in the arthritic diseases may also have a component of 'sensitization'. Sensitization is the concept that a person may experience

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a heightened sensitivity to pain which is mediated by continuous firing of peripheral nociceptors, often long after the initial noxious stimulus has been produced [5]. Ongoing activation of central brain pain processing pathways by peripheral stimuli has been described as central sensitization [6]. In this article, we explore the evidence for sensitization in rheumatic diseases and consider what this means for our understanding of rheumatic diseases and implications for future management.

Evidence for sensitization in rheumatic disease

Historically, researchers have used patient-reported outcome measures (PROMS) to report pain. These include visual analogue scale (VAS) [7], Likert scales for pain [8], the Western Ontario and McMaster osteoarthritis index (WOMAC) [9] and other scores measuring components of physiology which may be co-factors for pain, for example, depression and fatigue. Newer scores such as the Forgotten Joint Score [10] introduce a new aspect to patient-reported outcome following joint arthroplasty: the patient's ability to forget the artificial joint in everyday life.

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Factors including depression and anxiety can be measured using the Beck Depression Inventory [11] and function using the Health Assessment Questionnaire (HAQ) [12] in conjunction with pain scores. More recently, questionnaires which can be used to measure pain in a broader sense by people with arthritis include the painDETECT questionnaire [13], which has hitherto been used in other painful conditions, for example, fibromyalgia, back pain. Such questionnaires have revealed how the traditional boundaries between inflammatory pain and neuropathic pain (pain arising from the CNS itself) have become blurred, and multiple components could play a part in sustained pain reporting in people with arthritis, often despite use of combination therapies at significant economic and healthcare support costs [14].

Wylde *et al.* [15] undertook a comprehensive assessment of pain modalities in people with OA using quantitative sensory testing (QST), including light touch thresholds, thermal sensation thresholds, thermal pain thresholds and pain pressure thresholds (PPT) in people with knee OA and normal controls. Their findings showed that pressure algometry was the least variable measure of QST, and that other QST modalities including temporal summation and temperature measurements are more variable than QST measures over time in the same subject. A recent meta-analysis by Suokas *et al.* [16] has also addressed the use of pain pressure algometry in assessing pain in OA. The meta-analysis confirmed that people with OA have lower PPTs than normal non-OA populations and was replicated across studies. The lower PPTs were detected at affected and unaffected sites, suggesting that central sensitization contributes to pain in OA. Future work is now needed to establish which structural changes in the arthritic joint are most correlated with sensitization, since it is known that plain radiography does not correlate with features of sensitization measured by PPT in arthritic joints [17].

Measurement of PPTs and patient-reported tools for sensitization, for example, the painDETECT score, have also been tested in RA. Pollard *et al.* [18] showed that some people with RA have a phenotype that correlates with pain measured by PPTs, and correlated with other features of disability, including the HAQ, fatigue, depression and anxiety. Pain predominant features in RA are sometimes described as 'fibromyalgic' RA. We have also recently shown, using the painDETECT questionnaire, which in people with RA established on DMARD therapies, there continue to remain high levels of reported pain, despite use of analgesic drugs and suppression of inflammation [19]. We demonstrated that the majority of people with established RA for at least 5 years duration, maintained on DMARDs for inflammatory RA disease who had a mean disease activity score (DAS28) in remission of 2.09 ± 0.96, still had evidence high levels of pain reporting detected by VAS and painDETECT [19]. Furthermore, our RA subjects who reported the highest level of pain by VAS (54–100 mm) were the same group who also reported higher scoring on painDETECT measures, with a mean and standard deviation of 12.74 ± 4.46, compared with the low pain group (VAS 0–30 mm) who had a mean and standard deviation painDETECT score of 2.84 ± 1.30. Our data and results from RA populations in other groups also suggest that a proportion of subjects with RA are 'sensitized' to pain.

It remains to be seen whether inflammatory changes in the joint, for example, synovitis and erosions, overlap with sensitization pathways, or whether certain features of inflammation can be uncoupled from sensitization components. Such observations will be important for future treatment. For example, synovitis is often treated with DMARDs and nonsteroidal anti-inflammatory drugs. Another component of disease pathophysiology implicated in pain perception in arthritis are bone marrow lesions, and some groups have suggested their modulation with bone-targeted

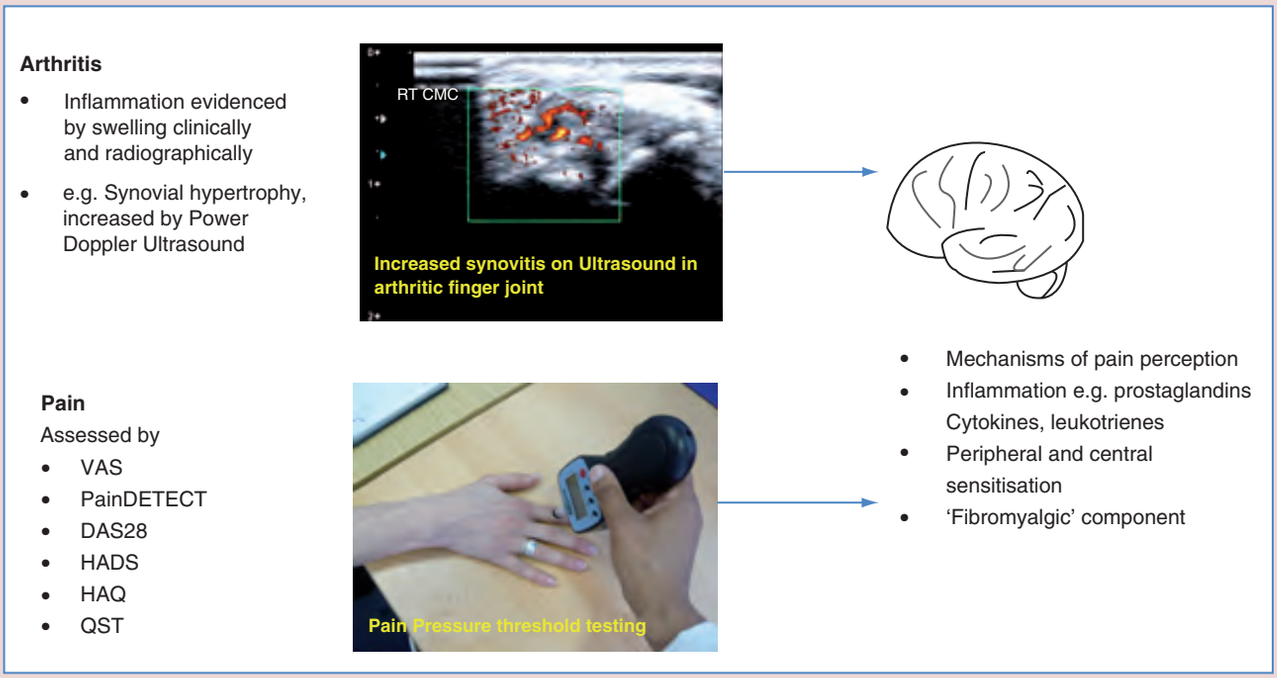

Figure 1. Summary of current concepts in factors mediating pain during arthritis. There is a recent recognition that the clinical features of inflammation and pain may not be a linear process in arthritis. Some features of pain could be partially uncoupled from inflammation in arthritic conditions. Other factors, distinct from inflammation, could also have an impact on pain reporting, including depression, anxiety and fatigue. Such components may contribute to pain 'sensitization', which can be measured using QST techniques such as painDETECT and PPTs.
PPT: Pain pressure threshold; QST: Quantitative sensory testing.

therapies, for example, bisphosphonates, but as yet we do not know if bisphosphonates are effective for bone pain related to OA [20].

Future answers to several of the questions outlined above may lie in studies which are able to quantify the degree of joint damage, for example, by MRI and the level of sensitization observed (Figure 1). Sensitization can currently be measured using a number of techniques, including QST, painDETECT and more recently, brain functional neuroimaging. The latter technique has been used by our group and others to detect sensitization in hand OA [21], knee OA [22] and in RA [23]. We have found increased activation of central brain processing centers in people with hand OA using functional neuroimaging localized to the insula, cingulate, thalamus and somatosensory cortex [21], which are all recognized brain pain processing ceners. Other groups have demonstrated similar regions of brain activation, including the prefrontal limbic system and basal ganglia, using functional brain MRI (fMRI) techniques in people with chronic knee OA [22]. Wartolowska *et al.* [23] have used structural MRI analyses with surface-based style morphometry analysis to show an increase in the gray matter content in the basal ganglia of RA patients [23]. Future work is now needed to decipher the relation between local changes occurring at the joint level, and the temporal sequence of central sensitization, which is likely to be influenced by numerous factors including duration of disease, level of local tissue inflammation, depression and anxiety. Only by gaining a deeper understanding of the interplay between such factors can we hope to understand disease pathophysiology to improve patient pain phenotyping, which could lead to improved treatments for the future.

Psychological aspects as well as structural abnormalities may also contribute to pain perception [24]. Subject-specific cognitive and emotional processes determine how pain is perceived in a chronic pain scenario, which may exacerbate catastrophizing and kinesiophobia [25]. Conversely subjects who do not see pain as a threat, who do not suffer from anxiety or depression, may continue to perform their daily activities and are more likely to improve [25,26]. Preliminary evidence also suggests that a reduction of catastrophizing and kinesiophobia is associated with a clinically relevant change in pain intensity and disability [27].

Implications for future management

An important question that has arisen from the work described includes to what extent we should be broad-

ening our measurement of pain modalities in the clinical setting. The DAS28-P [28], which is the proportion of DAS28 derived from the patient-reported components of the VAS and tender joint count, has been used by some researchers to assess the tender joint count and VAS components of the DAS28 score. It has also been suggested that the HAQ, HADS and painDETECT should perhaps be collected more routinely to assess factors contributing to arthritic pain. By using a composite score of such measures, we may reach a stage where patients' symptoms, including pain, can be phenotyped more distinctly from measures of inflammation such as synovitis, the erythrocyte sedimentation rate, C-reactive protein and imaging modalities and used to assess what individual patient treatment needs might be using a personalized approach.

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