Central hypersensitivity – A model for persistent musculoskeletal pain in inflammatory bowel diseases

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\begin{abstract}
Pain is reported to affect over 70\% of individuals with inflammatory bowel diseases (IBD), with abdominal and musculoskeletal (MSK) pain representing the most common complaints. MSK pain is typically considered within the narrow framework of inflammatory extraintestinal manifestations of IBD, resulting in a limited scope for the nature and underlying mechanisms participating in MSK pain experiences in this population. Symptoms related to central sensitization have recently demonstrated association with active IBD and worse MSK pain experiences, suggesting a potential role for central mechanisms in MSK-related pain. Current literature exploring persistent pain in chronic inflammatory and MSK populations propose complex pain models comprised of dynamic nervous system relationships influenced by primary disease features and concomitant pain states, as well as affective and cognitive components. Nervous system contributions in the development and maintenance of persistent pain are postulated to include mechanisms of peripheral and central sensitization, changes in descending central modulation, as well as structural brain changes. These models go beyond current MSK pain models described in IBD literature, highlighting the need for new frameworks for considering MSK-related pain in IBD. Consequently, this paper proposes a broader theoretical model whereby central mechanisms, such as central sensitization and grey matter structural brain changes. These models go beyond current MSK pain models described in IBD literature, highlighting the need for new frameworks for considering MSK-related pain in IBD.

\end{abstract}

\section*{Introduction}

Inflammatory bowel diseases (IBD), including Crohn’s disease and ulcerative colitis, are chronic inflammatory disorders of the gastrointestinal tract [1–4]. In addition to characteristic gut symptoms, pain is a commonly reported symptom which affects over 70\% of IBD patients, with abdominal and musculoskeletal (MSK) pain representing the most common pain complaints [5–9]. MSK pain is typically considered within the framework of extraintestinal manifestations (EIMs), a group of comorbidities with known associations to IBD. Although EIMs encompass a broad range of conditions affecting nearly every organ system, MSK manifestations are reported to be the most common EIM in IBD [10–12].

While current literature describes several MSK-related EIMs, such as: arthropathies (inflammatory and non-inflammatory), osteoporosis, and tendinopathies [13–15], to date inflammatory arthropathies are by far the most studied MSK-related EIM in IBD. This may be related to the fact that inflammatory arthropathies are classified as primary EIMs, distinguished as such by the underlying inflammation common to both IBD and other inflammatory manifestations [11]. The precise aetiology giving rise to inflammatory arthropathies in IBD patients is not well understood. However, three broad patterns for inflammatory arthropathies are recognised in IBD: peripheral arthritis strongly correlated with active gut inflammation (Type I), peripheral arthritis independent of gut inflammation (Type II), and axial arthropathies including the spine and sacroiliac joints which are also independent of IBD activity [4–6,11]. As clinical practice reflects focused consideration of inflammatory manifestations, it is unsurprising that common pathways for managing MSK pain in IBD include clinical assessment and treatment of inflammatory features and active IBD [6,11,16].

Although inflammatory arthropathies are predominantly considered in IBD literature, a recent investigation of joint pain in IBD demonstrated that 87.7\% of study participants with self-reported back/joint pain did not satisfy inflammatory diagnostic criteria [9]. These patients were categorized as having arthralgia, therefore suggesting that the majority of joint pain in IBD is potentially non-inflammatory in nature. Furthermore, numerous reports and guidelines regarding MSK-related EIMs state that arthralgia is more common in IBD than primary inflammatory arthritis [9,17,18]. Unfortunately, despite this understanding, previous studies investigating joint pain in IBD typically
exclude non-inflammatory pain or mention it without further investigation [5]. As a result, the scope and nature of MSK pain in IBD remains unclear with limited understanding of underlying mechanisms and moderating factors [5]. This narrow focus when considering MSK pain has led to incomplete management pathways, leaving many patients without treatment strategies for their pain. As a result, further investigation and expanded theoretical pain models are required in this population.

Hypothesis.

In order to address this current deficit in understanding of MSK-related pain in IBD, we undertook an exploratory analysis of self-reported MSK pain in individuals with IBD through subgrouping analysis [19]. The aims of this study were to explore mechanistic features of self-reported MSK pain as well as associations of demographics, comorbidities, and IBD characteristics. This study identified three clinically relevant subgroups of MSK pain experiences in IBD, where IBD activity and symptoms related to central sensitization were strongly associated with measures indicating worse MSK pain experiences. Interestingly, further analysis indicated that the predictive relationship between IBD activity and worse MSK pain experiences was significantly mediated by symptoms related to central sensitization.

Central sensitization is understood to be an increase or amplification of neural responsiveness within the central nervous system which can lead to pain hypersensitivity [20,21]. Peripheral injuries and/or inflammatory processes are believed to trigger changes in both peripheral and central nervous systems (PNS/CNS) which may lead to the neuroplastic changes seen in persistent pain states [22,23]. In the absence of a gold standard to directly identify central sensitization, diagnostically surrogate markers assessing a range of clinical and experimental characteristics are commonly used, including somatosensory functioning and factors influencing pain perceptions [20]. For instance, quantitative sensory testing is widely used to evaluate the excitability of different neural pathways/mechanisms to provide an understanding of pain modulation through facilitation and inhibition processes [24]. A common paradigm regarding sensory testing in this manner is that pain evoked by a non-noxious stimulus in non-injured tissue is assumed to be the result of CNS hypersensitivity.

In addition to altered somatosensory function, psychological factors (e.g., mood disorders, stress, etc.) have been identified as important determinants of pain experiences in both acute and chronic conditions [25–28]. As a result, evaluation of cognitive and affective features are commonly used to explore modulation of pain perceptions and nociceptive transmission [26]. Mechanisms by which psychological factors modulate pain experiences are complex. However, psychological factors have demonstrated an independent association with pain severity, disability, as well as neural hypersensitivity in multiple chronic pain [26,29,30] and healthy populations [26,31].

In this paper we hypothesize that exploration of central sensitization as part of a theoretical model for MSK pain in IBD will demonstrate altered somatosensory functioning in patients with MSK pain. This paper further hypothesizes that IBD activity and psychological features will be associated with altered somatosensory functioning and worse pain experiences. Consideration of contributions from central sensitization to persistent MSK pain experiences in IBD may support the development of effective and targeted treatment/assessment pathways. To explore the proposed relationships, a general overview of how inflammation contributes to the generation of persistent pain experiences may provide a foundation to consider MSK pain in IBD. Additionally, a review of previously described pain models from chronic inflammatory conditions, MSK conditions, and IBD literature will be used to propose a theoretical framework for considering central sensitization in IBD patients.

Inflammation and pain

The relationship between inflammation and pain is complex and involves multiple body systems. Inflammation is a fundamental biological process typically considered for its primary role in mounting an acute response against infections [32]. However, inflammatory processes also play a key role in a multitude of diverse chronic diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes, and IBD [32]. Regardless whether inflammation is a consequence of acute or chronic conditions, or is primarily regional versus systemic, it is well understood that the immune system interacts with the somatosensory system in the development of pain experiences [32]. Immune responses within both the PNS and CNS have been shown to result in the generation of pain states characterized by nociceptive, neuropathic, and/or central mechanisms [32]. Generally speaking, these pain states are distinguished according to the neuronal mechanisms involved in their pathogenesis.

The precise mechanisms through which inflammation initiates and maintains acute and persistent pain states are elaborate and go beyond the scope of this paper. However, it is generally understood that chemical mediators, including pro-inflammatory cytokines and chemokines, released by immune and glial cells during inflammatory processes sensitize and activate surrounding neurons [32–34]. Sensitization or activation of neurons by inflammatory mediators in this manner are described in both nociceptive and neuropathic models without primary injury or damage to the sensory axons [35]. In conditions such as IBD where inflammation can occur for prolonged periods, sensitization of neurons can promote long-term deleterious changes to multiple regions within the nervous system leading to pain experiences even after acute inflammation has resolved [32-34]. Pain persisting beyond periods of active inflammation, as well as pain experienced in regions away from the original site of inflammation, is understood to strongly correlate to changes within the CNS, including central sensitization and morphological changes to cortical grey matter in patient populations [32-34].

Chronic inflammatory and musculoskeletal pain models

Current paradigms for considering pain in chronic inflammatory and/or MSK conditions include the interpretation of peripheral nociceptive stimuli in the context of complex biopsychosocial experiences modulated through both the PNS and CNS [23]. Literature suggests that it is the activity within and between the PNS and CNS that collectively determine the dynamic and individual pain experience in persistent pain populations [23]. Primary investigations of chronic inflammatory and MSK pain conditions in non-IBD populations have described influences from psychosocial features, disease features, and importantly the potential for multiple pain mechanisms which overlap in their presentation [36–39]. For instance, in conditions such as ankylosing spondylitis and rheumatoid arthritis, it is not uncommon for patients to demonstrate both neuropathic and chronic widespread pain states, as a consequence of active inflammation and central mechanisms [40–43]. Persistent MSK pain conditions, such as osteoporosis and chronic joint pain, have similarly demonstrated multiple pain mechanisms with concurrent nociceptive and centrally driven pain states in observed patients [39]. Results from these investigations would suggest that frameworks focused on isolated mechanisms, such as inflammatory nociception, may over simplify the pathophysiology of pain in conditions such as IBD.

Pathways in the development and maintenance of persistent pain in both chronic inflammatory and MSK populations describe similar peripheral and central models. Classic peripheral models include inflammatory and/or mechanical activation of local nociceptive neurons in response to active inflammation and/or joint damage as part of disease processes [40]. Whereas central models describe amplified pain responses as a result of increased responsiveness of nociceptive
neurons, affective components, and cognitive features indicative of spinal and supraspinal changes in patient populations [23,42,43]. Consequently, as the role of PNS responses has been described in the progression of acute challenges to chronicity, peripheral and central pain mechanisms in both inflammatory and non-inflammatory conditions are understood to be closely intertwined [23,40].

**IBD pain models**

Over the past decade, models for chronic abdominal pain in IBD describe pain experiences beyond active inflammation seen in IBD flares, as well as pain experienced in other body regions, such as the back and legs [44,45]. This referred pain is thought to be the result of central sensitization causing an overlap in activity between visceral and somatosensory neurons within the spinal cord [44,45]. It is therefore unsurprising that models for chronic abdominal pain in IBD describe central mechanisms, such as central sensitization and modulation of descending inhibitory mechanisms, as a consequence of multiple pathways in IBD patients [44,45].

In addition to chronic abdominal pain, investigations of chronic postsurgical pain indicate that IBD patients are two to three times more likely to develop chronic pain following gastrointestinal surgery than non-IBD populations [46,47]. Central sensitization has been found to play a major role in the pathophysiology of chronic postsurgical pain, with its potentiation from prior disease inflammation thought to explain the increased prevalence of chronic pain in IBD patients [46,47]. Reports such as these suggest that central sensitization in conditions such as IBD represent nervous systems primed with the potential to generate amplified and/or persistent pain states from subsequent injury and/or systemic inflammation [48].

Contributions from altered affective and cognitive processing has been proposed in IBD abdominal pain models [45] as well as association to disease activity [49–51], implicating changes to higher brain centres [45]. For instance, the psychological paradigm related to how an individual appraises situations, described as an individual’s ‘perceived stress’ [52], has demonstrated significant association with disease activity [50,51] and reduced HRQOL [53] in IBD patients. Additionally, positive and negative emotional styles have been shown to be associated with somatogenic flares in IBD [50]. Interestingly, psychosocial constructs such as perceived stress and emotional styles have demonstrated similar association to altered somatosensory function in chronic pain [29] and asymptomatic [31] populations, suggesting a common basis for worse pain experiences in IBD patients.

**Central sensitivity syndromes**

Exploration of changes to higher brain centres seen in central sensitization has resulted in the identification of clinical populations termed ‘central sensitivity syndromes’ (CSS), such as irritable bowel syndrome (IBS), temporomandibular joint disorder, and fibromyalgia [54]. CSSs typically present with overlapping central sensitization features, such as: psychological distress, sleep disturbances, fatigue, pain, hyperalgesia, and hyperalgesia [54,55]. Previous investigations of CSS populations have suggested that individuals commonly present with multiple CSS disorders. For instance, approximately 70% of patients with fibromyalgia also presented with conditions such as IBS, and 65% of IBS patients also demonstrate primary fibromyalgia [56]. It is well understood that IBS is commonly seen in IBD, with reports of IBD patients in long-standing remission being two to three times more likely to have IBS than the general population [57]. Although the prevalence of fibromyalgia in IBD has not clearly been established, widespread pain has been reported in up to 49% of Crohn’s disease patients with IBS [58]. These findings highlight the significance of central sensitization in IBD, but also suggest that identification of CSS disorders in patient populations may also identify altered CNS activity potentially influencing MSK pain experiences as well.

**Cortical grey matter changes**

Neuroimaging studies investigating structural abnormalities of cortical grey matter have been performed in clinical populations, such as fibromyalgia [59], low back pain [60], IBS [61], ankylosing spondylitis [42], and Crohn’s disease [62,63]. Voxel-based morphometry in these populations have demonstrated grey matter changes in regions associated, for instance, with pain processing (e.g. cingulate, insulate, and prefrontal cortices) which have been linked to functional abnormalities related to pain modulation (facilitation and inhibition) as well as cognitive and emotional functioning [42,59,63]. Interestingly, one study investigating Crohn’s disease demonstrated a remarkable overlap in grey matter abnormalities also seen in chronic pain conditions, such as low back pain and fibromyalgia, suggesting a common basis [62]. Authors suggest that the structural brain changes seen in Crohn’s disease may account for pain complaints in patients demonstrating clinical disease remission [62].

Proposed mechanisms underlying grey matter changes in these populations include possible reduction in cell size, atrophy, and apoptosis from excitotoxicity and/or inflammatory mediators [59,60,62,64]. In chronic pain populations, for instance, the often excessive and ongoing neural inputs as a consequence of abnormal nociceptive/anti-nociceptive functions are thought to cause excitotoxicity resulting in neural loss [59,60,62,64]. Similarly, grey matter loss in IBD patients is also postulated to be related to excitotoxicity [62]. However, in IBD the assailing afferents are thought to be triggered by recurrent intestinal inflammation [62]. Additionally, the overproduction of inflammatory mediators seen in IBD has been proposed as another mechanism underlying grey matter changes [62]. Circulating inflammatory cytokines are thought to directly inducing neural apoptosis and decreased neurogenesis through signals which may be projected to several cortical and subcortical regions of the brain [62,65].

**Model for chronic MSK pain in IBD**

As outlined above, current literature exploring persistent pain in chronic inflammatory and MSK populations propose complex pain models comprised of dynamic nervous system relationships influenced by primary disease features and concomitant pain states, as well as affective and cognitive components. Nervous system contributions in the development and maintenance of persistent pain are postulated to include mechanisms of peripheral and central sensitization, changes in descending central modulation, as well as structural brain changes. These models go beyond current MSK pain models described in IBD literature. Although conceptual models for chronic abdominal pain have been described in IBD [45], a broader framework for considering the participation of central mechanisms, such as central sensitization, in MSK-related pain is needed (Fig. 1).

**Conclusion**

The primary purpose of this paper was to consider the potential role of central sensitization in persistent MSK pain in IBD patients. Central sensitization has been proposed within a theoretical model (Fig. 1) for considering MSK pain experiences, including modulation from psychological and IBD related factors. Specifically, this paper hypothesizes that exploration of central sensitization in IBD patients will demonstrate altered somatosensory functioning in patients with MSK pain, and that IBD activity and psychological factors will be associated with altered somatosensory functioning and worse pain experiences. The authors will set about testing the proposed hypothesis in an upcoming cross-sectional study assessing somatosensory functioning across three study groups: 1) IBD patients without MSK pain, 2) IBD patients with MSK pain, and 3) health controls. Psychological, IBD, and MSK pain features will be assessed to explore between group differences, thereby providing further context for somatosensory profiles. Exploration of
central mechanisms, such as somatosensory, affective, and cognitive functioning, in the context of defining IBD features may provide not only a deeper understanding of the generation and maintenance of persistent MSK pain in IBD, but also highlight the need for new targeted management pathways in this population.

Declaration of Competing Interest

None.

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