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Overlapping Pathophysiology of Cutaneous Dysesthesia and Complex Regional Pain Syndrome

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ABSTRACT

Background: Cutaneous dysesthesia (CD) and complex regional pain syndrome (CRPS) commonly emerge as complications following orthopedic trauma or surgical procedures. Although these conditions are traditionally classified independently, increasing clinical evidence indicates substantial overlap in their underlying neuropathic, neuroimmune, and neuroplastic mechanisms, complicating their diagnosis and management. Objective: This narrative review aims to critically examine current evidence concerning shared pathophysiological mechanisms linking CRPS and CD, specifically focusing on small-fiber neuropathy, central sensitization, neuroimmune dysregulation, and maladaptive neuroplasticity, and to discuss the clinical implications of these overlaps in orthopedic care. Methods: A targeted literature search was conducted using PubMed, Medline, and Google Scholar databases, employing the following keywords: "complex regional pain syndrome", "cutaneous dysesthesia", "small-fiber neuropathy", "central sensitization", "neuroimmune dysfunction", and "maladaptive neuroplasticity." The review prioritized recent peer-reviewed original research, systematic reviews, and meta-analyses published within the past decade. Articles were critically assessed for methodological quality, clinical applicability, and relevance to orthopedic trauma and surgery-related pain syndromes. Key Findings: Analysis identified four central mechanisms consistently shared by CRPS and CD: 1) Small-fiber neuropathy defined by reductions in intraepidermal nerve fiber density and altered peripheral nociceptive signaling; 2) Central sensitization characterized by

hyperexcitability of spinal and supraspinal neurons, resulting in amplified and often disproportionate pain responses; 3) Neuroimmune dysfunction involving persistent elevations of pro-inflammatory cytokines and circulating autoantibodies that sustain chronic inflammation and pain; and 4) Maladaptive neuroplasticity, notably cortical reorganization secondary to limb disuse or immobilization, perpetuating chronic sensory abnormalities and pain perception. Clinical Implications: The intersection of these pathophysiological processes contributes significantly to diagnostic ambiguity in distinguishing CD from CRPS, often delaying accurate recognition and appropriate management. Orthopedic clinicians and pain specialists should consider adopting a mechanistic diagnostic framework to differentiate these neuropathic syndromes from conventional post-surgical pain, thereby facilitating timely, targeted therapeutic interventions. Conclusion: Understanding the overlapping pathophysiological mechanisms between CD and CRPS underscores the importance of adopting multidisciplinary, integrative diagnostic and therapeutic strategies within orthopedic settings. Future research efforts should prioritize the development of precise biomarkers, the integration of advanced neuroimaging modalities, and targeted therapeutic approaches to address specific neuropathic, neuroimmune, and neuroplastic mechanisms. These advances hold significant potential to enhance patient outcomes, reduce chronic pain incidence, and optimize functional recovery following orthopedic trauma or surgical interventions.

1. INTRODUCTION

Cutaneous dysesthesia (CD) and complex regional pain syndrome (CRPS) are frequently encountered in the aftermath of orthopedic trauma or surgery, where patients report pain and sensory changes that extend beyond the expected window of tissue healing. Despite being traditionally classified as separate conditions, both syndromes share overlapping symptom profiles that include burning pain, heightened sensitivity to touch or temperature, and dermatomal discomfort in the absence of visible tissue damage [1, 2]. This clinical resemblance often blurs diagnostic boundaries, contributing to delays in recognition and treatment [1, 2].

CRPS is characterized by a constellation of sensory, autonomic, and motor disturbances, which is commonly divided into two subtypes based on whether a definable nerve lesion is present [3]. CD, on the other hand, lacks formal diagnostic criteria and typically presents as a painful or irritating sensation localized to a specific cutaneous distribution, often without associated skin changes. While CRPS has been studied more extensively, the underrecognition of CD, particularly in postoperative settings, can lead to diagnostic uncertainty and missed therapeutic windows [4].

Within orthopedic care, management tends to focus on structural repair, often overlooking the complex interplay between nerve injury, immune dysregulation, and central nervous system plasticity. As a result, pain syndromes such as CD and CRPS are frequently treated with generalized analgesics like nonsteroidal anti-inflammatories (NSAIDs), which rarely address the underlying mechanisms of persistent neuropathic symptoms [4, 5]. Patients who do not respond to early interventions are often labeled as outliers when their symptoms may reflect a broader failure to identify shared neurobiological pathways.

This review synthesizes emerging research on the shared mechanisms driving CRPS and CD in the context of orthopedic trauma. Specifically, we examine how small-fiber degeneration, spinal sensitization, immune-mediated signaling, and cortical reorganization contribute to symptom persistence across both syndromes. By bringing these mechanisms into clearer focus, we aim to promote diagnostic frameworks that go beyond structural imaging and support more precise, mechanism-based care for patients recovering from injury or surgery.

2. METHODS

This review was based on a targeted search of the medical literature related to complex regional pain syndrome (CRPS) and cutaneous dysesthesia (CD), with a focus on how these conditions emerge following orthopedic trauma or surgery. We used three main databases—PubMed, Medline, and Google Scholar—and limited our search to articles published within the past ten years.

Search terms included combinations of "complex regional pain syndrome", "cutaneous dysesthesia", "small-fiber neuropathy", "central sensitization", "neuroimmune dysfunction", and "maladaptive neuroplasticity." These terms were selected to identify both condition-specific studies and research examining overlapping mechanisms involved in post-traumatic pain.

We included peer-reviewed articles that examined nerve injury, immune system activation, or changes in central nervous system function in the context of orthopedic recovery. This included original studies, systematic reviews, meta-analyses, and narrative reviews with mechanistic insight. Case reports, non-peer-reviewed material, and studies not clearly related to trauma or surgical outcomes were excluded.

Each paper was reviewed for clarity, scientific quality, and clinical relevance, particularly in relation to how pathophysiological mechanisms might explain persistent pain in patients whose imaging or surgical outcomes appear normal. Priority was given to studies that could help link basic biological findings with practical orthopedic care.

2.1. Shared Pathophysiological Mechanisms Linking Cutaneous Dysesthesia and Complex Regional Pain Syndrome after Orthopedic Trauma

This section examines the overlapping biological mechanisms that drive both cutaneous dysesthesia (CD) and complex regional pain syndrome (CRPS), focusing on four interrelated pathways that emerge following orthopedic trauma.

- **Small-Fiber Neuropathy After Orthopedic Trauma**

Cutaneous dysesthesia (CD) and complex regional pain syndrome (CRPS) are often treated as separate conditions, but they frequently arise after orthopedic trauma, and present with strikingly similar symptoms: burning, tingling, cold sensitivity, and persistent skin-based pain [2, 6]. CRPS is more widely studied and recognized, but CD is poorly defined and is often overlooked in clinical practice. Yet, there is increasing evidence that these conditions may have a common neurobiological basis: small-fiber neuropathy (SFN). SFN is characterized by damage to the small nerve fibers that are responsible for pain and temperature sensation, specifically the unmyelinated C fibers and thinly myelinated Aδ fibers [7]. If these fibers are injured, patients can have a variety of sensory symptoms that do not show up on standard nerve tests. In this section, we will discuss how the structural, immune, and clinical evidence positions SFN as a shared mechanism that helps explain why CRPS and CD often look so similar after trauma.

Despite the absence of formal diagnostic criteria, several focal dysesthetic syndromes reported in the neurologic and dermatologic literature offer clinically and mechanistically relevant analogues to CD [2]. Shumway *et al.* [2] describe conditions such as notalgia paresthetica, brachioradial pruritus, meralgia paresthetica, and trigeminal trophic syndrome, each of which often emerges following trauma, spinal pathology, or mechanical strain [2]. These syndromes consistently involve burning, tingling, or hypersensitive skin symptoms in dermatomal distributions, sometimes with evidence of reduced sensory thresholds, despite normal imaging and standard electrophysiologic findings [2]. These syndromes, like CD, often follow mechanical or surgical trauma and exhibit localized burning, tingling, and temperature sensitivity, features that are hallmarks of small-fiber neuropathy and mirror post-operative presentations in orthopedic setting [2].

Recent clinical case reports further reinforce this hypothesis. Oh *et al.* [8] described a patient who developed bilateral meralgia paresthetica following femoral cannulation, exhibiting localized paresthesia confirmed by sensory nerve conduction studies without CRPS features, highlighting iatrogenic small-fiber dysfunction as a distinct entity [8]. In a parallel case, Payne *et al.* [9] presented histopathologic evidence of demyelination, axonal loss, and regenerative clusters in a patient with meralgia paresthetica, directly linking these changes to dysesthetic symptoms and confirming a small-fiber pathology in a non-CRPS setting [9].

Moreover, Billig *et al.* [10] demonstrated that quantitative sensory testing (QST) can reliably predict intraepidermal nerve fiber density (IENFD) loss in patients with small-fiber neuropathy, providing a clinically accessible tool to support diagnosis in focal dysesthesia where biopsy may not be feasible [10].

Although not formally diagnosed as CD, these cases present with the same localized sensory features and post-traumatic onset observed in patients with CD, reinforcing the argument that such symptoms represent focal small-fiber neuropathy syndromes not captured by existing diagnostic frameworks. These findings, although drawn from conditions not labeled as CD, demonstrate the same mechanistic substrate—small-fiber degeneration—underlying localized, post-traumatic dysesthesia, reinforcing its plausibility as a primary driver in CD. Together, these findings indicate that cutaneous dysesthesia, particularly when emerging in the post-traumatic or post-surgical setting, may reflect a focal manifestation of small-fiber neuropathy that remains underrecognized due to the absence of overt structural lesions and limited integration of QST or biopsy into standard postoperative care.

Furthermore, the limitations of current diagnostic tools may contribute to this underrecognition. As Lauria *et al.* [11] emphasized, standard skin biopsy primarily detects somatic intraepidermal fibers and may fail to capture autonomic involvement, despite its relevance to CRPS and potentially CD [11]. This underscores the need for broader diagnostic consideration when patients present with localized, unexplained dysesthesia following surgery or injury, even if they do not meet full CRPS criteria.

- **Histopathological Evidence of Small-Fiber Degeneration**

The recognition of CRPS as a small-fiber neuropathy marked a major shift in how trauma-related pain is understood. In a pivotal study, Oaklander and Fields [7] used skin biopsies to show that patients with CRPS-I had a 29% reduction in intraepidermal nerve fiber density (IENFD), along with signs of microvascular damage and autonomic fiber loss [7]. These findings moved the field beyond earlier assumptions that CRPS was primarily a disorder of the central nervous system and highlighted the importance of localized peripheral nerve damage. Supporting this view, Yvon *et al.* [12] provided high-resolution evidence from a CRPS case in which the patient underwent limb amputation [12]. Their transmission electron microscopy (TEM) study revealed extensive degeneration in both large and small fibers [12]. Interestingly, Aδ fibers were mostly spared, while Remak bundles, clusters of unmyelinated C fibers wrapped by Schwann cells, were severely disrupted [12]. This imbalance may tip the pain system toward hypersensitivity, allowing remaining fibers to become overactive.

Rasmussen *et al.* [13] added another layer of complexity. Even though CRPS-I typically affects one limb, they found that IENFD was reduced bilaterally [13]. Using both sensory testing and biopsy, they identified small-fiber loss and altered temperature thresholds in both the injured and uninjured limbs [13]. This raised questions about whether CRPS is truly a localized disorder or if systemic or central mechanisms contribute more than previously thought. Unlike Rasmussen *et al.* [13], who observed widespread small-fiber loss [13], Lauria *et al.* [11] emphasized a more localized diagnostic strategy [11]. They reinforced that skin biopsy remains the go-to test for confirming SFN, especially when large-fiber studies do not explain symptoms [11]. But, they also noted its limitations: standard biopsy mostly detects somatic fibers and may overlook changes in the autonomic system, which is highly relevant in CRPS cases involving swelling, color change, or temperature shifts.

While both Lauria *et al.* [11] and Yvon *et al.* [12] document the potential for small-fiber regeneration following injury, symptomatic recovery is not always observed [11-17]. This raises the possibility, supported by broader theories of pain chronification, that central sensitization may persist even after peripheral nerve regeneration. Although neither study directly investigated central remodeling, their findings reinforce the need to consider how early peripheral nerve injury may initiate maladaptive processes that are more difficult to reverse in chronic stages. Clinically, this underlines the importance of timely identification of SFN in patients reporting atypical sensory symptoms, even in the absence of visible lesions or positive electrophysiological findings. Together, these studies suggest that SFN is not just a secondary consequence of CRPS or CD, it may be a root cause, and one that deserves greater diagnostic attention in trauma-related pain.

- **Peripheral Inflammatory and Immune Mechanisms**

While the initial mechanical trauma in CRPS and CD sets the stage for small-fiber damage, the body's

immune and inflammatory responses often prolong or worsen the injury. These responses can persist well after the tissue appears healed, creating a loop of chronic nociceptor sensitization and nerve fiber degeneration. Devarajan *et al.* [18] demonstrated this in a rodent fracture model [18]. They showed that keratinocytes near the injury site released proinflammatory cytokines, such as IL-1β and activated caspase-1, a key inflammasome protein [18]. This activity sensitized nearby C fibers, contributing to prolonged pain signaling [18]. While this study was based on animals, the mechanism they described mirrors clinical observations in CRPS, where skin and serum often show elevated inflammatory markers.

Wasner *et al.* [6] added a human dimension to this theory [6]. In their study of CRPS patients, they found significantly elevated levels of TNF-α and IL-6 in the affected limbs [6]. These cytokines were associated with hallmark CRPS symptoms like temperature asymmetry and vasomotor instability [6]. More notably, they proposed a mechanism where sympathetic nerve fibers begin to interact directly with nociceptors, a phenomenon known as sympathetically maintained pain [6]. In this model, pain fibers may become hypersensitive to circulating catecholamines, making stress or adrenergic stimuli amplify pain.

Dirckx *et al.* [19] explored a potential autoimmune contribution [19]. They found that 33% of CRPS-I patients tested positive for antinuclear antibodies (ANA), significantly higher than the 4% observed in healthy controls [19]. In contrast, 7.3% of CRPS-I patients tested positive for antineuronal antibodies, a rate comparable to the 7.5% seen in the general population [19]. While these findings do not confirm a pathogenic role for autoantibodies, they suggest that immune dysregulation may be present in a subset of patients. The authors hypothesized that autoantibodies could contribute to CRPS pathophysiology in certain individuals, though direct disruption of small fibers by these antibodies has not been demonstrated and remains speculative.

Each of these studies highlights a different pathway: keratinocyte-mediated inflammation, sympathetic-afferent signaling, and possible autoantibody involvement. Yet, they all converge on the same result of persistent damage to small fibers. These pathways may interact in additive or synergistic ways, helping to explain the heterogeneity of symptoms and disease progression seen in both CRPS and CD. This multifaceted immune response may explain why some patients continue to experience symptoms long after the original injury has healed. Moreover, it invites a broader rethinking of how persistent post-traumatic pain is approached in practice. Rather than viewing inflammatory changes as transient or self-limited, clinicians may need to consider their ongoing role in perpetuating SFN, particularly in cases where symptoms defy conventional diagnostic categories. Taken together, the literature supports that immune dysregulation is not simply a byproduct of SFN in trauma-related pain syndromes, but it is a driving force that can sustain or even worsen CRPS and CD over time.

2.2. Central Sensitization in Post-Traumatic Pain

Building on the previous discussion of small-fiber neuropathy (SFN), this section shifts focus to the central nervous system, where persistent peripheral input can reshape pain processing pathways and contribute to symptom persistence in both CRPS and CD [6, 18].

Following orthopedic trauma, persistent nociceptive input from injured tissues can lead to profound changes in how the central nervous system processes pain. This phenomenon, known as central sensitization, represents a state in which spinal and supraspinal neurons become hyperresponsive to both painful and non-painful stimuli [18]. This shift in processing may obscure the relationship between injury location and symptom distribution, complicating both diagnosis and treatment selection. In trauma-related neuropathies, central sensitization may develop secondarily to ongoing nociceptive input, potentially amplifying symptoms and obscuring the original site of injury [18]. This section examines the biological processes by which trauma-induced SFN contributes to spinal cord hyperexcitability and altered pain perception in both complex regional pain syndrome (CRPS) and cutaneous dysesthesia (CD).

A central mechanism often cited in CRPS involves increased excitability of dorsal horn neurons. Wasner *et al.* [6] reported thermal and mechanical hyperalgesia in CRPS patients that could not be explained by peripheral inflammation alone [6]. These findings suggest that persistent nociceptive input may alter

second-order neuron responsiveness and overwhelm inhibitory circuits, consistent with observations of spinal hyperexcitability [6]. These spinal-level changes are also thought to engage higher-order pain circuits, contributing to symptom complexity in both CD and CRPS. The authors further described how catecholamine sensitivity and vasomotor instability could result from abnormal sympathetic–afferent coupling, which itself may reflect spinal plasticity [6].

This spinal sensitization does not arise in isolation. Devarajan *et al.* [18], in their rodent model, demonstrated that persistent release of proinflammatory cytokines from keratinocytes, specifically IL-1β and caspase-1, sensitized C fibers in the periphery [18]. While the study focused on peripheral mechanisms, the authors proposed that sustained nociceptive input could reinforce spinal sensitization, a process often described as afferent barrage, supporting a "bottom-up" model of central gain [18]. While Devarajan's findings are limited to a preclinical model, they mirror the prolonged inflammatory signaling and escalation of symptoms observed in human CRPS. This process creates a feedback loop, where inflammation not only sustains peripheral sensitization, but acts as a primer for spinal hyperexcitability. This aligns with patient trajectories in both CRPS and CD, where symptoms often escalate from localized burning to widespread discomfort.

Evidence for central amplification also comes from Rasmussen *et al.* [13], who found bilateral reductions in intraepidermal nerve fiber density (IENFD) in patients with unilateral CRPS [13]. Unlike classic models of localized neuropathy, this systemic presentation of a typically unilateral disorder suggests a shift in the pain system's central processing. While the loss of peripheral fibers might initially reflect SFN, the persistence and spread of symptoms implicate a secondary central reorganization. This blurring of anatomical boundaries challenges the conventional belief that pain should map predictably to the site of injury.

Central circuit adaptation may also contribute to the prolonged sensory symptoms observed in CD [2]. Shumway *et al.* [2] reviewed several chronic dysesthesia syndromes, including brachioradial pruritus and notalgia paresthetica, which frequently arise after trauma, but persist without visible structural damage [2]. In these cases, persistent itching, burning, or tingling may reflect central amplification in response to a prior peripheral trigger [2]. Although direct neuroimaging was not part of the review, the chronicity and dermatomal patterning of symptoms strongly suggest that the central nervous system plays a sustaining role. These conditions suggest that even minimal or transient peripheral injury may trigger long-term central adaptations, particularly in vulnerable individuals. Such overlooked syndromes strengthen the argument that CD may be misclassified as a dermatologic condition when it could be considered a manifestation of malfunctioning central pain processing.

Taken together, findings from Devarajan *et al.* [18], Wasner *et al.* [6], Rasmussen *et al.* [13], and Shumway *et al.* [2] illustrate how persistent input from injured small fibers, whether from orthopedic trauma or other localized insults, can trigger and maintain central sensitization. This process may begin in the dorsal horn but often expands into broader neural circuits, affecting perception, autonomic function, and emotional regulation. For patients with CD and CRPS, central sensitization offers a compelling explanation for why symptoms often escalate in intensity and distribution over time, even in the absence of ongoing peripheral damage. Recognizing this dynamic helps shift the clinical lens from purely structural diagnoses to more systems-based assessments, where both peripheral and central mechanisms are considered essential to understanding chronic pain after trauma. Understanding central sensitization is crucial for accurate diagnosis and avoiding mislabeling chronic CD and CRPS symptoms as functional or psychogenic.

2.3. Maladaptive Neuroplasticity Following Limb Disuse or Immobilization

In the aftermath of orthopedic trauma or surgical intervention, clinical recovery often requires the injured limb to remain immobile for extended periods. Immobilization may be externally imposed—through casting, bracing, or surgical protection—or internally maintained through behavioral avoidance, guarding, or fear of pain. Irrespective of the mode, sustained limb disuse disrupts normal sensory feedback to the central nervous system. When afferent input to cortical sensory circuits is chronically diminished, the somatosensory cortex may undergo topographic reorganization that alters how the body is internally represented. This process, known as maladaptive neuroplasticity, is increasingly recognized as a significant

contributor to the persistence of pain in conditions, such as complex regional pain syndrome (CRPS) [16]. Though cutaneous dysesthesia (CD) has not yet been evaluated to the same extent as CRPS, parallels in its emergence following trauma or immobilization support the hypothesis that similar cortical mechanisms may be involved.

The clearest evidence for cortical remodeling arises from functional neuroimaging in CRPS. In a landmark functional magnetic resonance imaging (fMRI) study, Pleger *et al.* [17] demonstrated that patients exhibited markedly reduced activation in the contralateral primary somatosensory cortex (S1) during stimulation of the affected limb [17]. The extent of this reduction was strongly associated with impaired tactile discrimination and increased pain severity [17]. These findings support that representational loss in S1 is not merely epiphenomenal, but may act as a mechanistic driver where degraded somatosensory maps yield a mismatch between incoming afferent signals and internally predicted sensory feedback.

This hypothesis has been reinforced by broader syntheses. Di Pietro *et al.* [18], in a meta-analysis of fifteen studies across multiple imaging modalities, reported that the most consistent feature was a reduction in S1 map size, particularly in studies employing non-noxious digit-specific input [18]. While other variables, such as activation strength, latency, and inhibition, showed greater inconsistency, the convergence around reduced representational area highlights afferent deprivation, rather than nociceptive intensity, as a key factor [18]. These principles are particularly relevant in the context of CD, where immobilization and behavioral disuse may similarly deprive cortical circuits of patterned sensory input.

However, not all investigations have replicated these findings. In a high-resolution fMRI study, Mancini *et al.* [16] reported that the cortical area, location, and geometry of S1 digit maps in CRPS patients were largely comparable to those of both the unaffected limb and healthy controls [16]. This stands in contrast to the conclusions drawn by Di Pietro *et al.* [18] and raises the possibility that earlier reports of map compression may have reflected methodological artifacts, such as low spatial resolution or indirect measures of cortical distance [16]. At the group level, no significant differences were detected, and inter-individual variability did not correlate with clinical severity. These results suggest that cortical reorganization in CRPS may be more heterogeneous than previously assumed and underscore the importance of methodological rigor in neuroplasticity research.

The reversibility of such cortical changes has been most clearly demonstrated in the context of phantom limb pain. In the sensory homunculus, the representation of the lips—central to functions such as speech and eating—has been shown to encroach upon the primary somatosensory cortex (S1) area formerly devoted to the amputated hand [20]. Birbaumer *et al.* [20], using EEG source localization, observed that in amputees who experienced pain relief following regional anesthesia, this aberrant cortical remapping was substantially reversed, with the S1 hand region regaining its prior boundary [20]. In contrast, no such reversals were observed in patients who did not report analgesia [20]. This within-subject link between pain modulation and somatosensory reorganization reinforces the notion that topographic plasticity is not only functionally relevant but also therapeutically responsive.

Although CD has not been directly studied with functional imaging, clinical analogues suggest similar underlying processes. Shumway *et al.* [2] described syndromes such as notalgia paresthetica, brachioradial pruritus, meralgia paresthetica, and trigeminal trophic syndrome, each of which frequently follows regional trauma, spinal pathology, or prolonged mechanical strain [2]. These focal conditions typically present without observable skin or nerve lesions, exhibit resistance to conventional treatment, and often develop after periods of postural restriction or biomechanical stress [2]. Across these entities, a consistent pattern emerges: chronic dysesthetic symptoms follow localized afferent disruption or disuse in the absence of peripheral injury [2]. This pattern, strongly reminiscent of CRPS, supports the hypothesis that CD may likewise involve central maladaptation and justifies investigation into its cortical correlates.

The spatial disruption of somatosensory maps in CRPS may also extend beyond S1, affecting higher-order association areas involved in limb localization and body schema. Karin *et al.* [19], using EEG and source modeling, found abnormal activation in the posterior parietal and premotor cortices of CRPS patients during motor imagery tasks [19]. These regions are essential for maintaining an internal model of the body, sometimes described as an "expanded cortical footprint", which integrates sensory input with motor

planning and ownership [19]. Disruptions in these circuits may explain phenomena, such as vague limb perception, neglect-like symptoms, and postural avoidance. Karin *et al.* interpreted these findings as evidence of impaired sensory-motor integration that may persist despite peripheral recovery [19]. Recognizing this expanded cortical footprint provides a mechanistic rationale for targeting higher-order processing in treatment. In support of this approach, Pleger *et al.* [17] observed that mirror therapy and tactile discrimination training were associated with pain reduction and S1 map re-expansion, while Birbaumer *et al.* [20] demonstrated that pain relief through anesthesia produced rapid shifts in cortical representation [17, 20]. These findings suggest that recalibrating distorted internal models and restoring functional body ownership may be feasible through non-invasive, centrally directed therapies.

Finally, the reversibility of these maladaptive changes reinforces the therapeutic potential of addressing cortical circuits directly. In addition to their sensory retraining findings, Pleger *et al.* [17] demonstrated that cortical changes can be functionally reversed even in chronic cases, while Birbaumer *et al.* [20] confirmed the dynamic plasticity of S1 under real-time modulation [17, 20]. For CD patients with post-immobilization symptoms, such therapies may offer meaningful benefit despite the absence of peripheral pathology. While further study is warranted, these observations provide a neurobiological rationale for non-pharmacologic, cortex-focused treatment strategies in both CRPS and CD.

Taken together, the evidence suggests that disuse-induced cortical reorganization represents a central mechanism through which post-traumatic pain may become self-sustaining. Both CRPS and CD may be perpetuated by similar patterns of sensory-motor disintegration, which strengthens the rationale for investigating cortical plasticity as a shared therapeutic target. As subsequent sections will explore, this cortical vulnerability may interact with neuroimmune mechanisms and central sensitization, compounding symptom persistence and complicating recovery.

2.4. Neuroimmune Dysfunction and Autoimmunity in Orthopedic Pain Syndromes

Pain that lingers after orthopedic trauma, especially in patients diagnosed with cutaneous dysesthesia (CD) or complex regional pain syndrome (CRPS), is often difficult to explain using structural findings alone. Increasingly, both clinicians and researchers are turning their attention to immune system dysfunction as a possible explanation for symptoms that persist even after surgical recovery or fracture healing. In both CD and CRPS, immune disturbances have been reported at multiple levels, including elevated local inflammatory mediators and circulating autoantibodies [18, 21]. These abnormalities are often unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs), suggesting that cyclooxygenase-driven inflammation is not the only process involved [4, 5]. This section explores two immunological pathways that may help explain ongoing symptoms in these conditions: 1) dysregulated local neuroimmune signaling and 2) systemic autoimmune activity.

- **Local Neuroimmune Activation**

In CRPS, abnormal immune activity has been observed in the skin and surrounding nerve structures [21]. Studies have documented elevated levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and mast cell infiltration in affected tissue [21]. These findings correspond closely with hallmark CRPS symptoms, such as burning pain, temperature sensitivity, and mechanical allodynia [21]. CD patients often report similar symptoms despite the absence of clear structural nerve injury, which raises the possibility of shared immune mechanisms across the two conditions [2].

On a cellular level, the pain response appears to become amplified through sustained interactions between immune cells and nociceptors. Neurons release neuropeptides like substance P and CGRP, which stimulate mast cells and keratinocytes [18]. In response, these immune cells produce cytokines that heighten the sensitivity of nociceptors [18]. This feedback loop can intensify pain signaling over time, potentially converting a temporary injury into a chronic pain state [18]. While this specific pathway has not been formally confirmed in CD, the clinical overlap suggests a comparable neuroimmune mechanism may be involved.

Even when there is no infection present, the immune system may still mount a response to surgical

trauma or tissue damage. Molecules released during ischemia or injury, known as damage-associated molecular patterns (DAMPs), can bind to toll-like receptors (TLRs) on immune cells [19]. Although this process is initially adaptive, prolonged activation may lead to chronic inflammation and pain. In this way, unresolved immune signaling could help explain persistent pain in CD and CRPS patients after apparent healing [19].

Emerging evidence also suggests that dysesthesia and allodynia may follow different resolution trajectories after nerve injury, which complicates treatment decisions and reflects the heterogeneity of immune involvement. A recent 2023 clinical study of patients undergoing brachial plexus decompression by García-Jeronimo *et al.* reported that positive sensory symptoms such as allodynia and burning pain persisted in a subset of patients despite adequate surgical relief of nerve compression [22]. This disconnect between structural correction and residual dysesthesia supports the notion that immune-mediated or centrally maintained processes may prolong sensory symptoms beyond the initial injury context [22]. Additional support for immune heterogeneity comes from a systematic review by Knudsen, Santoro, Bruehl, Harden, and Brunner [23], which identified multiple clinical subtypes of CRPS based on inflammatory biomarkers, symptom clusters, and disease trajectory [23]. The review emphasized that some CRPS subtypes are characterized by marked systemic immune activation, while others demonstrate a more localized or centrally driven pathophysiology, further reinforcing the argument for immunophenotypic variability within CRPS that has not yet been paralleled in CD [23].

While both CRPS and CD have been associated with sensory hypersensitivity and dysesthetic pain, current evidence suggests that immune system abnormalities are more robustly characterized in CRPS. Multiple studies have demonstrated that CRPS involves measurable alterations in both local and systemic immune function, including elevated levels of TNF-α and IL-6, increased mast cell infiltration, and the presence of autoantibodies in a significant subset of patients [18, 19, 24]. These findings support the notion that CRPS can involve both innate and adaptive immune activation, potentially contributing to its complex and relapsing clinical course [18]. In contrast, there is currently limited direct evidence that cutaneous dysesthesia is associated with systemic immune dysregulation. Most of what is known about CD comes from case series and reviews of focal syndromes, such as notalgia paresthetica and brachioradial pruritus, that lack systemic inflammatory markers or cytokine profiles [2]. Any immune contribution to CD is likely to be localized, neurogenic, or secondary to mechanical nerve irritation, rather than reflecting a broader immunopathologic process [2]. Therefore, while CD and CRPS may share clinical features and downstream neuroinflammatory consequences, immune abnormalities are more clearly and extensively documented in CRPS [19, 24]. This disparity likely reflects not only biological variation but also the more extensive immunophenotyping conducted in CRPS research [23]. Whether this represents a true mechanistic distinction or simply reflects the limited immunophenotyping of CD remains an open question.

- **Autoimmunity and Circulating Autoantibodies**

In some patients with CRPS, systemic autoimmune features have also been identified. Elevated levels of antinuclear and antineuronal autoantibodies have been reported, targeting cellular components within the nervous system [19]. These immune responses may interfere with nerve signaling and lead to longer-term changes in pain perception through glial activation and immune pathway sensitization [18].

Although the pathogenic role of these autoantibodies remains uncertain, their presence has prompted the exploration of immunomodulatory therapies such as intravenous immunoglobulin (IVIG). The clinical rationale for IVIG in CRPS is not solely dependent on antibody specificity; rather, IVIG is thought to exert broader immunoregulatory effects [18]. These may include suppression of pro-inflammatory cytokines, modulation of B-cell activity, or interference with Fc receptor signaling on innate immune cells [18]. Given that a subset of CRPS patients report symptom improvement following IVIG administration, even in the absence of a clear autoantibody target, the therapy is considered reasonable in select refractory cases [18].

Some CRPS patients with overlapping features of small-fiber neuropathy have shown partial improvement with plasma exchange therapies, an approach typically used in autoimmune disorders [25]. These observations suggest that, for a subset of patients, immune-mediated mechanisms may contribute directly to their symptoms. While this has not yet been confirmed in CD, the resemblance in clinical course and

treatment resistance supports the possibility that autoimmune involvement may also play a role. Given the symptom similarity and resistance to conventional treatment, it is plausible that a subset of CD patients may exhibit comparable autoimmune profiles that have not yet been systematically investigated.

One proposed model suggests that physical trauma may initiate immune reprogramming in genetically predisposed individuals [18]. This cascade could involve persistent B-cell activity, complement system activation, and heightened glial reactivity [18]. Together, these changes may support chronic pain states in the absence of ongoing structural injury [18].

A 2022 systematic review and meta-analysis by Mahmoud, Hamza, and Zayid analyzed outcomes of various treatment modalities for CRPS following hand surgery and found that immunomodulatory agents, particularly bisphosphonates and IVIG, were among the few interventions demonstrating consistent pain reduction in randomized controlled trials [26]. These agents appeared to outperform conventional pharmacologic therapies such as NSAIDs and corticosteroids, which showed more variable efficacy across studies [26]. The authors noted that therapeutic success often required multimodal strategies that addressed both peripheral inflammatory and central sensitization mechanisms; an approach that aligns with emerging models of CRPS pathophysiology incorporating immune, neural, and autonomic components [26]. While the review stops short of formalizing a treatment hierarchy, its findings underscore the need for integrated care pathways that combine immune-targeted therapies with neuromodulatory or rehabilitative strategies in select patient subtypes [26].

- **NSAIDs Resistance as a Clinical Signal of Immune Dysregulation**

Although NSAIDs remain a mainstay in managing acute inflammation following orthopedic procedures, their limited success in chronic pain syndromes suggests additional mechanisms may be at play. In patients with CD or CRPS, symptoms frequently persist despite extended use of NSAIDs [4]. This pattern raises the possibility that prostaglandin inhibition alone is insufficient in cases where immune dysfunction, neurogenic inflammation, or sensitization of pain pathways may be driving persistent symptoms. Chunduri and Aggarwal [5] similarly note that NSAIDs often fail to address pain involving central sensitization and non-COX-mediated immune signaling, further reinforcing the need to explore alternative therapeutic targets [5].

Incorporating advanced diagnostic tools such as skin biopsy and quantitative sensory testing (QST) into routine clinical workflows may enhance early identification of small-fiber neuropathy in patients presenting with persistent dysesthetic symptoms following orthopedic injury. Patients reporting burning pain, allodynia, or temperature sensitivity beyond standard surgical recovery windows may benefit from QST, which serves as a noninvasive method to detect functional impairment in small sensory fibers, as outlined in the European Federation of Neurological Societies (EFNS) guidelines [27]. When QST reveals abnormalities, a skin biopsy can be used to confirm intraepidermal nerve fiber density loss, in accordance with consensus guidelines jointly issued by the EFNS and the Peripheral Nerve Society [11]. Incorporating these diagnostic measures into post-operative evaluation, especially in patients who fail to respond to NSAIDs, who exhibit atypical pain distributions, or in whom immune-mediated or neuropathic mechanisms are suspected, may facilitate earlier recognition of underlying neuropathic processes and expedite referral to neurology or pain medicine specialists. These tools are already implemented in many neurology and pain centers, which supports their feasibility for integration into interdisciplinary orthopedic follow-up care. Broadening access to these assessments may reduce the risk of pain chronification and help tailor mechanistically specific treatments for post-surgical dysesthesia.

Immune system dysfunction, at both local and systemic levels, may help explain the prolonged pain seen in CD and CRPS patients following physical trauma. These mechanisms often remain undetected by conventional imaging or lab testing but have significant clinical consequences. A deeper understanding of the neuroimmune and autoimmune pathways involved may lead to better diagnostic strategies and more effective, individualized treatment options for post-traumatic pain syndromes.

Together, the mechanisms outlined in this section, ranging from peripheral fiber degeneration to central sensitization, cortical maladaptation, and immune-mediated amplification, reflect the multifactorial nature of post-traumatic pain in CD and CRPS. While each process operates along distinct biological pathways,

their overlap reveals a shared vulnerability to persistent nociceptive signaling after orthopedic injury. Understanding how these systems interact provides a foundation for reevaluating current treatment limitations and guiding more targeted approaches in the clinical management of these patients.

2.5. Clinical Implications and Outcomes

Patients recovering from orthopedic trauma or surgery sometimes face lingering pain syndromes like complex regional pain syndrome (CRPS) and cutaneous dysesthesia (CD) that do not respond well to standard treatments [7]. As discussed in previous sections, small-fiber degeneration, central sensitization, and neuroimmune dysregulation all play roles in these conditions [18, 28, 29]. These mechanisms help explain why pain may persist even after structural healing, although more evidence is needed to clarify their long-term interactions and individual contributions.

This section introduces three proposed approaches—low-dose naltrexone (LDN), intravenous immunoglobulin (IVIG), and neuroplasticity-based rehabilitation—that aim to target specific biological disruptions implicated in CRPS and CD. While data remain limited, especially for LDN and neuroplasticity-based rehabilitation, IVIG has shown promise in select CRPS populations [27, 30]. Although not universally effective, these interventions are being explored as part of a broader effort to align treatment choices with suspected underlying mechanisms.

To translate mechanistic insights into improved outcomes, interdisciplinary care for post-traumatic pain syndromes should be guided by structured clinical workflows involving orthopedic surgeons, neurologists, and pain specialists. For example, orthopedic teams may initiate early screening, while neurologists confirm diagnostic findings and pain specialists tailor treatment plans. Orthopedic teams are often positioned to recognize early signs of dysesthesia, such as burning pain, cold sensitivity, or allodynia, that persist beyond expected recovery timeframes [7, 11, 18]. While six to eight weeks post-surgery may serve as a general guideline, this timeframe may vary based on individual recovery patterns [11]. In more severe or rapidly escalating cases, earlier referral may be appropriate.

At that point, patients could be referred for quantitative sensory testing or neurology evaluation to assess for small-fiber neuropathy or related abnormalities [10, 27]. Neurologists can confirm findings using tools like skin biopsy or QST [11], while pain specialists may initiate therapies from commonly used classes such as SNRIs, gabapentinoids, or immune-modulating agents when appropriate.

To support collaboration, interdisciplinary teams might consider shared documentation templates and joint follow-up protocols, particularly when first-line treatments are insufficient. Tools such as EMR flags for unresolved neuropathic symptoms or structured "post-op pain rounds" are proposed strategies to improve real-time coordination. These could include automated consult prompts in orthopedic follow-up notes or standardized checklists to track ongoing neuropathic features. Although these tools are not yet widely implemented, they may help detect chronic pain trajectories earlier and promote shared responsibility in prevention. Structural barriers such as knowledge gaps, care silos, and reimbursement constraints continue to hinder care integration. These limitations mirror broader systemic obstacles described in interdisciplinary care research [31]. Future initiatives may include piloting structured interdisciplinary programs with embedded feedback mechanisms to evaluate outcomes, provider coordination, and care quality over time. Expanded interdisciplinary training and continuing education may also help address provider-level barriers and promote broader adoption of shared-care frameworks.

- **Low-Dose Naltrexone: A Neuroimmune Modulator**

Low-dose naltrexone (LDN) has gained attention for its role in calming inflammation in hard-to-treat pain conditions. Unlike its high-dose form used in addiction medicine, LDN (around 4.5 mg) blocks toll-like receptor 4 (TLR4) on microglial cells, which reduces the release of pain-promoting cytokines like IL-6 and TNF-α [32]. Instead of dulling pain by sedation or masking it, LDN may target a key driver of persistent pain: neuroinflammation.

A small case series on CRPS reported fewer flare-ups and improved mobility after starting LDN [33]. Broader trials in fibromyalgia showed measurable drops in pro-inflammatory cytokines and pain after eight

weeks of use [34]. While LDN has not been directly studied in CD, its potential benefits may extend to CD based on shared neuroimmune features with CRPS and fibromyalgia. Especially for orthopedic patients with persistent pain post-healing, this could represent a non-opioid path forward.

- **IVIG: Targeting Autoimmune Triggers**

Intravenous immunoglobulin (IVIG) offers a different route to address CRPS and CD, namely through immune modulation. Some patients with CRPS test positive for circulating autoantibodies, and IVIG appears to help by neutralizing these and downregulating other immune responses. In a randomized trial, IVIG reduced pain intensity by an average of 1.55 units compared to saline ($P < 0.001$), with 42% of patients experiencing a median reduction of at least 2 points, and three individuals reporting a 50% or greater reduction in pain [30]. Earlier open-label studies cited in the same document found that approximately half of the patients experienced a 30% or greater pain reduction. While encouraging, these findings come from small samples and are influenced by variability in placebo response.

The treatment has broad immunomodulatory effects, including calming cytokines, blocking complement, and suppressing immune cells such as T-cells. This could be useful in postoperative patients who show signs of systemic immune dysregulation. However, IVIG may not benefit every patient, particularly those without evidence of autoantibody involvement, but it remains a potentially valuable option for carefully selected cases. Although the pairing of IVIG with low-dose naltrexone (LDN) has not been directly studied, their complementary mechanisms, including IVIG's systemic immunomodulatory effects and LDN's ability to modulate glial cell activity, may together offer a dual approach to managing persistent pain, particularly in cases lacking clear structural pathology.

- **Neuroplasticity Rehabilitation: Restoring Functional Networks**

Neuroplasticity-targeted rehabilitation has been proposed as a promising strategy to reverse maladaptive changes in CRPS and potentially CD. While most evidence comes from CRPS studies, structural and functional neuroimaging has revealed alterations in the somatosensory cortex, motor areas, and parietal regions involved in pain processing, movement coordination, and body schema representation [35], which may be relevant to CD as well. These cortical disruptions are thought to contribute to abnormal sensorimotor perception, dysesthesia, and distorted limb representation observed in these conditions.

Task-specific rehabilitation combined with neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS) or transcutaneous direct current stimulation (tDCS), has been shown to facilitate motor and sensory recovery in CRPS. Zangrandi *et al.* [35] describe how these techniques may "normalize the maladaptive brain plasticity responsible for CRPS chronicization" and enhance the brain's responsiveness to paired rehabilitative therapies [35]. By improving cortical excitability and sensorimotor integration, these strategies may help restore function in patients with chronic post-traumatic pain.

Importantly, early implementation of neuroplasticity-directed treatments may prevent cortical changes from becoming entrenched. Longitudinal imaging studies have shown that resolution of CRPS symptoms is associated with reversal of gray matter abnormalities, reinforcing the value of timely intervention and rehabilitation-focused care.

- **Integrating a Multimodal Approach**

Taken together, LDN, IVIG, and neuroplasticity-focused rehab align closely with the mechanistic disruptions previously discussed. These include neuroinflammation, autoimmunity, nerve injury, and cortical reorganization. They aim not just to mask pain, but to intervene at its origin.

Orthopedic teams and pain specialists might consider using this triad as a foundation for managing persistent postoperative pain. Each therapy addresses a different layer of the problem. While these treatments have not yet been evaluated in combination, they target distinct mechanisms, and may form the foundation of a future multimodal strategy tailored to each patient's profile. With more investigation, these strategies could help reduce suffering, restore function, and lower the long-term burden of unresolved orthopedic pain.

2.6. Challenges and Limitations in Diagnosis and Classification

- **Lack of Reliable and Accessible Biomarkers**

A central limitation in the recognition of these conditions is the persistent absence of reliable and accessible biomarkers. Most conventional orthopedic imaging techniques, including X-rays and magnetic resonance imaging (MRIs), are designed to detect gross anatomical abnormalities such as fractures or joint pathologies. However, they fail to capture the subtle pathophysiological changes that characterize small-fiber neuropathy (SFN), including intraepidermal nerve fiber degeneration. Advanced techniques, such as skin biopsy and quantitative sensory testing (QST), have demonstrated strong diagnostic utility for SFN, with skin biopsy regarded as the current gold standard due to its high sensitivity and specificity [2, 34]. Despite their promise, these methods remain underutilized in orthopedic care due to multiple barriers, including limited physician training, restricted access, and systemic institutional inertia [34].

- **Underrecognition of Cutaneous Dysesthesia (CD)**

The diagnostic challenges are further compounded by the limited awareness of CD as a legitimate neuropathic entity. Unlike CRPS, CD lacks formal diagnostic criteria, and its symptoms (burning, tingling, or painful skin sensitivity localized to post-surgical dermatomes) are often dismissed as dermatologic irritation or attributed to psychosomatic distress. As Shumway *et al.* [2] emphasize, CD remains under-recognized in orthopedic and general medical settings, leading to delayed workup for small-fiber injury or central sensitization [2]. This misrecognition parallels early experiences with CRPS and reflects a broader need for classification systems that account for localized dysesthetic syndromes without full CRPS presentation.

- **Limitations of Current Classification Criteria**

The inadequacy of current classification criteria represents another major limitation. Current CRPS diagnostic frameworks, while more refined than earlier models, may still exclude patients with partial or atypical presentations, particularly those who do not meet the full constellation of sensory and autonomic signs. Dirckx *et al.* [19] have shown considerable heterogeneity in CRPS biomarker profiles, including patients with and without detectable autoantibodies [19]. Such diagnostic fluidity complicates treatment access and underscores the need for spectrum-based models that recognize gradations of neuroinflammatory, autonomic, and sensory involvement. Without this flexibility, patients straddling the CRPS-CD boundary may fall through diagnostic and therapeutic gaps.

- **Unaddressed Mechanisms: Central Sensitization and Neuroimmune Crosstalk**

The transition from acute nociception to chronic neuropathic pain is mediated in large part by central sensitization and neuroimmune amplification. Cytokines, such as IL-1β, IL-6, and TNF-α, play a key role in this progression by acting on nociceptive neurons and glial cells, lowering the threshold for pain transmission and enhancing excitability in dorsal horn and thalamocortical circuits [2, 34]. Malcangio [36] outlines how these molecular interactions not only contribute to pain amplification but also sustain it in the absence of peripheral injury [36]. Importantly, these mechanisms are not typically targeted by standard post-operative regimens, which focus on tissue healing and often rely on opioids that may inadvertently exacerbate hyperalgesia [35].

- **Gaps in Functional and Electrophysiologic Diagnostics**

This mismatch between pathophysiology and clinical practice is further underscored by imaging studies in CRPS patients. Functional neuroimaging has revealed heightened activation in the somatosensory cortex, premotor regions, and anterior insula, all of which are involved in pain modulation, emotional response, and body schema representation [37]. These findings align with Zangrandi *et al.* [35], who observed that maladaptive cortical reorganization, including altered excitability in the motor cortex and sensory-parietal integration centers, maintains pain perception and disrupts sensorimotor recovery in a way that is difficult to reverse [35]. When diagnosis is delayed, these neuroplastic changes become less reversible, contributing to chronicity and treatment resistance.

Moreover, a growing body of literature has emphasized the importance of electrophysiological and neurophysiologic markers in distinguishing neuropathic from non-neuropathic pain early in the postoperative period. Pessoa *et al.* [37] demonstrated that contact heat-evoked potentials (CHEPs) and central conduction testing can detect central sensitization and thalamocortical disinhibition in patients with CRPS, potentially offering an objective biomarker for diagnosis [37]. These techniques offer neurophysiological

insight into pain signaling dynamics, but remain absent from most orthopedic diagnostic workflows, which continue to prioritize structural imaging over functional assessment. However, despite their promise, these tools remain rarely integrated into orthopedic workflows.

- **Absence of Predictive and Preventive Frameworks**

The lack of predictive frameworks for identifying at-risk individuals also limits proactive care. While Jensen and Finnerup [38] do not explicitly identify pre-existing pain disorders, anxiety, or genetic susceptibility as predictive factors for CRPS or CD, they do report that early sensory hypersensitivity, such as hyperesthesia following surgery, can increase the odds of persistent pain in other neuropathic conditions, including central pain after spinal cord injury or post-stroke pain [38]. These findings indirectly support the rationale for risk stratification, even if formal criteria do not yet exist for CRPS or CD. Nevertheless, these early warning signs are rarely integrated into orthopedic protocols, resulting in a reactive rather than preventative model of care, where neuropathic diagnoses are only considered after symptoms become chronic and entrenched.

- **Therapeutic Lag and Limited Clinical Integration**

Finally, the broader clinical management landscape presents additional barriers. As previously discussed, interventions, such as low-dose naltrexone, intravenous immunoglobulin, or neuromodulation align with core mechanisms of CRPS and CD, but remain underused due to regulatory ambiguity, cost constraints, and clinician unfamiliarity. Delayed recognition of neuroimmune contributions to pain can reduce the effectiveness of these therapies, emphasizing the need for earlier integration into postoperative care.

In summary, the diagnosis and classification of postoperative neuropathic pain syndromes, such as CRPS and CD, are hindered by structural, conceptual, and mechanistic limitations. The absence of accessible biomarkers, inconsistent classification systems, and limited use of neurophysiologic tools restrict early recognition. At the same time, failures to assess risk factors, integrate newer diagnostics, or revise criteria can delay care. Addressing these gaps will require broader awareness across orthopedic disciplines, expanded access to advanced diagnostics, and the development of flexible classification models that reflect the pathophysiologic continuum linking CRPS and CD.

2.7. Future Directions

As the clinical recognition of CRPS and CD evolves, several research directions may help close longstanding diagnostic and therapeutic gaps. These include molecular biomarkers, functional imaging techniques, and more nuanced classification systems tailored to the heterogeneity seen across postoperative neuropathic pain syndromes. While current strategies often rely on symptom patterns and exclusion-based diagnoses, future approaches may benefit from integrating mechanistic insights into routine care.

- **MicroRNAs and Gene-Regulatory Biomarkers**

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression post-transcriptionally. By binding to complementary sequences in messenger RNA, they can block translation or promote degradation, thereby influencing immune signaling and inflammatory processes [39]. Their regulatory role has led to growing interest in their potential as biomarkers in chronic pain conditions. Reinhold *et al.* [40] examined miR-223 and miR-939 in patients with CRPS and found that lower levels of miR-223 were associated with poor response to treatment [40]. While these early findings suggest miRNAs may reflect persistent neuroinflammation, their diagnostic application remains investigational. Broader validation across surgical and trauma-exposed populations will be essential, especially in patients with focal dysesthesia who do not meet formal CRPS criteria.

- **Cytokine Dynamics and Immune Phenotyping**

A growing body of work has also focused on cytokines and immune cell signaling as predictive tools for persistent pain. In a longitudinal human study, Sluka *et al.* [41] observed that elevated interleukin-6 (IL-6) following surgery was associated with an increased likelihood of developing chronic postsurgical pain [41]. These cytokine shifts, if detectable early in recovery, may provide an objective means of identifying high-risk patients. Although CD has not been studied as extensively as CRPS in this context, the sensory

overlap between conditions makes immune profiling a plausible avenue for future investigation. Kollmann *et al.* [42] highlighted the role of bone-related biomarkers in CRPS, including increased bone turnover and histological changes in cortical and trabecular bone [42]. Their findings included elevated levels of osteoprotegerin, calcitonin, alkaline phosphatase, and deoxypyridinoline, alongside cortical thinning and altered marrow vascularity. These observations suggest that bone remodeling may contribute to deep, aching pain and sensory abnormalities in CRPS [42]. While similar patterns have not yet been demonstrated in CD, future studies may benefit from investigating whether localized changes in bone metabolism also play a role in the persistence of dysesthetic pain following surgery or trauma.

Emerging research also suggests that bone remodeling and inflammatory bone turnover may contribute to the pathophysiology of CRPS. In a comprehensive review, Kollmann *et al.* [42] reported elevated levels of osteoprotegerin, calcitonin, and deoxypyridinoline, along with histological changes such as cortical bone thinning and vascular alterations in the bone marrow [42]. These findings indicate active bone turnover and suggest that skeletal processes may be linked to the deep, aching pain commonly described in CRPS. While these mechanisms have not been studied in CD, the potential involvement of osteocyte signaling in other postoperative pain syndromes warrants further investigation. Exploring whether similar bone-related changes occur in patients with focal dysesthesia could clarify the basis for non-dermatomal, persistent pain that is not easily explained by superficial nerve injury alone.

- **Imaging-Based Characterization of Neural Injury**

Emerging imaging methods may improve the detection of structural and functional changes in patients with neuropathic pain who lack overt radiographic findings. Although most imaging studies have focused on CRPS, similar neuroplastic processes may underlie persistent pain in CD. Diffusion tensor imaging (DTI) offers one such tool. In a study of patients with chronic pain, Hotta *et al.* [43] reported white matter alterations within somatosensory and motor pathways, suggesting that prolonged nociceptive signaling may induce reorganization at the microstructural level [43]. These imaging changes, if correlated with clinical outcomes, could eventually support the identification of neuroplastic subtypes within CRPS and CD. Positron emission tomography (PET) imaging may also provide insights into the spatial dynamics of inflammation [44]. Cropper *et al.* [44] demonstrated that, in a mouse model of CRPS, activated macrophages persisted at peripheral injury sites even after central microglial activity subsided [44]. This is particularly relevant for CRPS and potentially CD, where inflammatory pain may persist despite structural recovery. This temporal separation highlights the potential of PET tracers to monitor ongoing immune processes beyond the spinal cord and brainstem.

Further upstream, preclinical work by Soderblom *et al.* [45] has introduced three-dimensional imaging methods capable of reconstructing axonal projections and their relationship to fibrotic scar tissue [45]. Although these techniques currently rely on tissue-clearing agents and genetic labeling in rodent models, they offer a foundation for developing imaging protocols that capture small-fiber loss with spatial resolution. Such tools could eventually complement traditional histology and improve the specificity of CD diagnosis, which remains a clinical construct without objective confirmation.

- **Classification Frameworks and Translational Models**

Despite increasing recognition of post-traumatic dysesthesia as a spectrum disorder, classification criteria for both CRPS and CD remain rigid and exclusionary. Mangnus *et al.* [46] proposed a tiered approach to diagnosis that accounts for pain phenotype, symptom duration, and response to treatment [46]. This framework supports the transition from binary diagnostic labels to a spectrum-based model, allowing inclusion of patients with partial small-fiber injury, regional dysesthesia, or autonomic features who may not meet strict CRPS criteria. Experimental models may also aid in refining diagnostic boundaries. Brewer *et al.* [47] examined cutaneous denervation in rats following quisqualate injections, which overstimulate glutamate receptors and produce localized sensory loss [47]. Their work supports the use of focal neurochemical injury as a platform for studying CD-like conditions in controlled settings. While translation from animal models to human classification must be cautious, these systems provide a way to isolate mechanisms like peripheral nerve loss, receptor sensitization, and behavioral hypersensitivity.

3. CONCLUSIONS

Cutaneous dysesthesia and complex regional pain syndrome represent two difficult-to-classify entities that frequently emerge after orthopedic injury or surgical repair. Despite the absence of gross anatomical findings, a growing body of evidence now supports their shared neurobiological basis, including small-fiber neuropathy, central sensitization, neuroimmune activation, and maladaptive cortical reorganization. In this review, we synthesized current evidence supporting the shared pathophysiology of these disorders, with an emphasis on their relevance in post-traumatic clinical settings.

Building on these mechanistic insights, we proposed an interdisciplinary framework for clinical detection, diagnostic workup, and tailored therapy. Structured collaboration among orthopedic surgeons, neurologists, and pain specialists offers the most promising path forward. We proposed a model built on symptom-based referral triggers, EMR-driven coordination, and interdisciplinary reassessment protocols. Addressing the structural barriers to implementation, such as limited reimbursement models, knowledge gaps, and fragmented communication, will be essential for translating this approach into real-world care.

Finally, we evaluated three emerging therapies, low-dose naltrexone, intravenous immunoglobulin, and neuroplasticity-based rehabilitation, as representative examples of mechanism-specific interventions. While these strategies are not universally effective, they target key drivers of symptom persistence and may offer a more rational treatment pathway than trial-and-error prescribing.

As the orthopedic field evolves to recognize the complexity of post-traumatic pain syndromes, bridging mechanistic understanding with interdisciplinary care delivery may help reduce misdiagnosis, improve function, and lessen the chronic burden of unresolved pain. By positioning cutaneous dysesthesia and CRPS within a unified diagnostic and mechanistic framework, this review also underscores the urgent need for standardized classification tools that better capture the clinical reality of post-traumatic neuropathic pain. Future research should prioritize longitudinal studies, expanded neurophysiological profiling, and biomarker-driven diagnostics to support early identification and targeted treatment. In doing so, the field may move closer to resolving longstanding diagnostic ambiguity and unlocking more precise, mechanism-informed treatment strategies for these often-overlooked conditions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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