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Peripheral Nociceptor Input and Central Sensitization in Fibromyalgia: A Systematic Review and Meta-Analysis

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Abstract

Fibromyalgia (FM) is a prevalent nociplastic pain disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbance, and cognitive impairment. Central sensitization (CS), amplified pain processing within the central nervous system, is widely accepted as a core mechanism in FM pathophysiology. Whether ongoing peripheral nociceptor input is required to initiate and sustain CS in established FM remains controversial, despite evidence of subtle inflammation, muscle or metabolic abnormalities, and small-fiber pathology. This systematic review and meta-analysis integrate mechanistic and observational evidence from quantitative sensory testing, local anesthetic blocks, small-fiber neuropathy (SFN) studies, muscle and microcirculatory assessments, and markers of low-grade inflammation to reappraise the peripheral contribution to CS. Findings from local anesthetic block studies show that tonic peripheral input can dynamically modulate and maintain CS in some individuals, whereas the frequent observation of SFN (approximately 50%) and emerging metabolic or inflammatory data suggest clinically relevant peripheral drivers may define distinct FM phenotypes. Debate persists over the relative importance of peripheral versus central mechanisms, the clinical relevance of SFN, and the impact of minor peripheral changes when overt pathology is absent. Clarifying these issues has important implications for patient stratification and personalized treatment. The review underscores the need for high-quality longitudinal trials that simultaneously track peripheral and central sensitization dynamics, to illuminate the dynamic interplay between peripheral pathology and central pain amplification in FM.

This review was retrospectively registered with PROSPERO (CRD420251077548).

Keywords

Fibromyalgia, Central Sensitization, Nociplastic Pain, Peripheral Nociceptive Input, Small-Fiber Neuropathy

Introduction

Fibromyalgia (FM) is a chronic nociplastic pain syndrome that affects approximately 3–6 percent of the global population, with a clear female predominance [1]. Beyond widespread musculoskeletal pain, patients commonly experience non-restorative sleep, persistent fatigue, and cognitive dysfunction, all of which impose substantial functional limitations. Recent diagnostic work suggests that incorporating deep tendon reflex responses may improve clinical assessment of FM [2].

Since the original tender point era, the mechanistic focus has shifted away from primary muscle pathology toward altered pain processing within the central nervous system (CNS); contemporary frameworks therefore classify FM among the central sensitization syndromes (CSS) [3]. Early studies with intravenous lidocaine infusions likewise pointed to a peripheral modulatory component in FM pain. Central sensitization (CS) denotes heightened responsiveness of CNS nociceptive neurons to normal or even subthreshold afferent input, clinically evident as hyperalgesia and allodynia. Whether CS in established FM is maintained autonomously or remains dynamically modulated by ongoing peripheral nociceptor input remains contested. Proposed peripheral contributors include small fiber pathology (SFP), low-grade neuroinflammation, and subtle metabolic or microischemic muscle changes [4]. Clarifying the relative influence of these peripheral drivers is essential for accurate patient stratification and the development of phenotype-guided treatment strategies [5].

Methods

(This study was conducted as a systematic review and meta-analysis in accordance with PRISMA 2020.)

Protocol and Registration

This systematic review and meta-analysis adhered to the PRISMA 2020 guidelines. A PROSPERO record was created retrospectively for transparency (CRD420251077548), but the review was not prospectively registered.

Eligibility Criteria

Population:

Adults (≥18 years) with fibromyalgia diagnosed by any version of the American College of Rheumatology (ACR) criteria (1990, 2010/2011, or 2016).

Exposure:

Objective assessment of small fiber pathology using either skin punch biopsy with intraepidermal nerve fiber density (IENFD) quantification or in vivo corneal confocal microscopy (CCM).

Outcomes:

Studies were eligible if they reported the prevalence of abnormal IENFD or CCM findings (either directly or derivable from available data).

Study Designs:

Cross-sectional studies, observational cohorts, or baseline data from interventional trials with ≥10 fibromyalgia patients.

Exclusion Criteria:

Studies with <10 participants, pediatric cohorts, non-English articles, studies reporting only continuous nerve density without prevalence data, abstracts without full-text publication, and animal or in vitro studies.

Data Sources and Search Strategy

We conducted comprehensive electronic searches in PubMed/MEDLINE, Embase (via Ovid), and Web of Science Core Collection (SCI-Expanded) from January 1, 2013, to March 31, 2024. Searches were limited to English-language studies involving human adults. The initial search was performed on April 1, 2024, and updated on March 31, 2024.

Full strategies for all databases are available in Supplementary Table-S1. We also searched ClinicalTrials.gov and the WHO ICTRP for unpublished studies, reviewed conference abstracts from ACR and EULAR (2013–2024), and conducted backward and forward citation screening in Google Scholar and Scopus. We did not include unpublished dissertations or theses.

Study Selection

Search results were deduplicated in EndNote 21 and screened in Rayyan.ai. Two reviewers (MA and AD) independently screened titles/abstracts and full texts. Disagreements were resolved through discussion or adjudication by a third reviewer (HNC). Reasons for exclusion at full-text review were documented. The PRISMA 2020 flow diagram is presented in (**Fig-1**) (935 records screened; 8 studies included in meta-analysis).

Data Extraction

Data were extracted using a piloted Excel form capturing study design, population characteristics

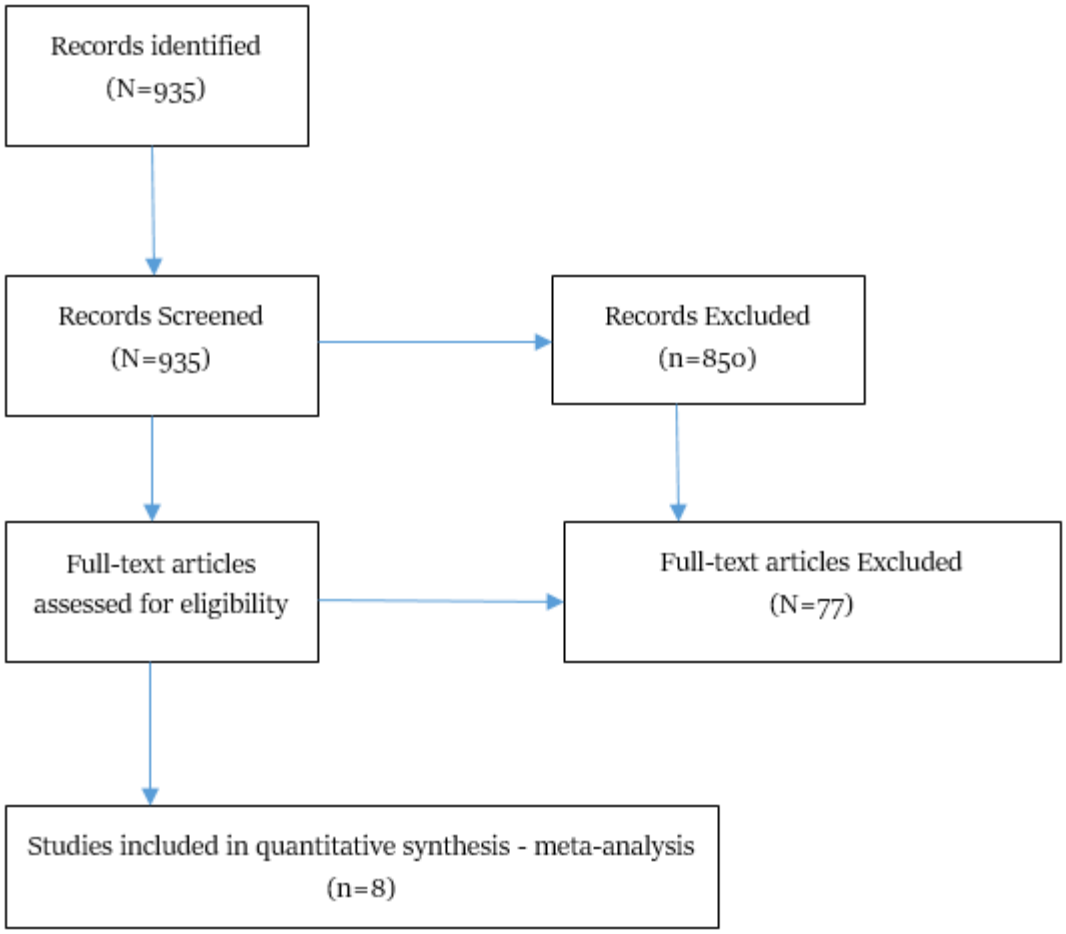

Fig-1: PRISMA 2020 study-selection flow diagram

A total of 935 records were identified and screened at title/abstract level. Eight-hundred-fifty records were excluded during this initial screening. The remaining 85 full-text articles were retrieved and assessed for eligibility; 77 of these full texts were excluded (e.g., wrong population, outcome, or study design), leaving 8 studies that met all inclusion criteria and were therefore incorporated into the quantitative synthesis (meta-analysis).

IENFD/CCM methods, diagnostic cutoffs, prevalence data, and secondary outcomes (e.g., pain scores, functional measures) when available. Two reviewers performed extraction independently, with discrepancies resolved by consensus.

Risk of Bias

We assessed methodological quality using the Joanna Briggs Institute (JBI) Checklist for Prevalence Studies (9 domains). Each item was rated as low, moderate, or high risk of bias. Interrater reliability was assessed qualitatively; discrepancies were resolved by consensus without formal κ statistic calculation.

Statistical Analysis

Prevalence estimates were stabilized using the Freeman-Tukey double arcsine transformation and pooled using a DerSimonian–Laird random effects model in R (meta and metafor packages) [6]. Heterogeneity was evaluated using Cochran's Q and I^2 statistics, with thresholds of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. Planned subgroup analyses included IENFD vs CCM prevalence and sex-based prevalence differences. Sensitivity analyses excluded high-risk studies and applied Hartung-Knapp adjustments. Publication bias was assessed via funnel plots and Egger's test when ≥10 studies were available.

Certainty of Evidence

The overall certainty of the pooled prevalence estimate was graded using the GRADE approach, implemented in GRADEpro GDT.

Narrative Synthesis of Local Anesthetic Block Studies

Due to significant heterogeneity in block technique, duration, and outcome measures, studies involving local anesthetic interventions were synthesized narratively, with results presented descriptively in terms of direction and magnitude of effect.

Identification of Local Anesthetic Studies

Local anesthetic block studies were identified through a supplementary targeted search conducted in PubMed and Google Scholar using combinations of terms such as "fibromyalgia," "lidocaine," "nerve block," and "peripheral injection." We also used backward citation tracking from included reviews and forward citation alerts on key articles (e.g., Staud et al., Sorensen et al.). No formal search string was developed for this secondary aim, given the limited number and methodological variability of eligible studies. This approach aligns with narrative synthesis principles described in PRISMA-S guidelines.

Software and AI Assistance

EndNote 21 and Rayyan.ai were used for reference management and screening. Meta-analyses were conducted in R (version 4.3.2) using the meta and metafor packages. Language refinement and formatting assistance were provided by a large language model (ChatGPT, OpenAI GPT-4o), with all final content reviewed and verified by the authors.

Results

Small-Fiber Pathology (SFP) Prevalence:

Pooled data from Grayston et al. (2019) demonstrated that approximately half of patients with fibromyalgia (FM) exhibit evidence of small fiber pathology (SFP), with a pooled prevalence of 49 percent (95 percent confidence interval [CI]: 38–60; I^2 = 68 percent, indicating moderate heterogeneity). Subgroup analyses indicated variations in prevalence according to diagnostic technique: skin biopsy methods yielded a prevalence of 45 percent (95 percent CI: 32–59; I^2 = 70 percent), whereas corneal confocal microscopy (CCM) methods reported 59 percent (95 percent CI: 40–78; I^2 = 51 percent) (see **Table-1**). The observed heterogeneity (I^2 = 68 percent) likely reflects methodological variations across the included studies [7].

Local Anesthetic Block Studies:

Four key studies evaluating local anesthetic blocks in FM consistently reported clinically meaningful short-term pain relief in a substantial subset of patients. Intramuscular lidocaine injections at tender points resulted in response rates of approximately 45–46 percent [8]. Similarly, targeted nerve blocks involving accessory and transscapular nerves provided sustained relief (≥24 hours) in 58 percent of patients [9]. Intravenous lignocaine infusions demonstrated

Table-1: Prevalence of Small-Fiber Pathology in Fibromyalgia

Subgroup	Studies (n)	FM Patients (N)	Prevalence (%)	95% CI (%)	I^2 (%)	Heterogeneity p-value
All (Skin Biopsy + CCM)	8	222	49	38–60	68	<.001
Skin Biopsy Only	5	~180	45	32–59	70	0.003
CCM Only	3	~120	59	40–78	51	0.047

Grayston et al. (2019) report Cochran's Q-test p-values for the overall set of eight studies (p < .001), for the skin-biopsy subgroup (p = .003), and for the CCM subgroup (p = .047).

Table-2: Selected Local Anesthetic Block Studies in Fibromyalgia

Study (Year)	Block Type	FM Patients (N)	Response Rate (%)	Responders (k)	p-value	Response Criterion
Hong & Hsueh [8]	Intramuscular Lidocaine	20	45%	9	0.0888	≥30% pain reduction (1–2 hrs)
Staud et al. [13]	Intramuscular Lidocaine vs Placebo	24	46%	11	0.0598	≥30% immediate pain reduction
Lari & Kodumudi [9]	Accessory + Transscapular Nerve Blocks	12	58%	7	0.0232	≥30% sustained relief (≥24 hrs)
Sorensen et al. [11]	IV Lidocaine Infusion (5 mg/kg)	30	50%	15	0.0142	≥50% pain reduction (~7 days)

Footnote: One-sided binomial test versus a 30 percent null hypothesis.

reproducible pain reductions in crossover designs [10], while additional series confirmed ≥50 percent relief lasting up to seven days for about half of patients [11]. Parallel work on cytokine and chemokine profiling supports the presence of peripheral immune signatures distinguishing FM from controls [12] (**Table-2**).

Discussion

This systematic review and meta-analysis confirm that central sensitization (CS) remains a pivotal feature of fibromyalgia (FM), while highlighting substantial evidence supporting a meaningful peripheral contribution in certain patient subgroups. Consistent findings of approximately 49 percent small fiber pathology (SFP) prevalence across various methodologies, especially skin biopsy (45 percent) and corneal confocal microscopy (59 percent), underscore that peripheral nociceptive abnormalities significantly coexist with central mechanisms.

Preliminary evidence from a small number of local anesthetic block studies tentatively supports this interpretation. While methodological limitations preclude definitive conclusions, the overall consistency in both direction and magnitude of effect across the four heterogeneous trials suggests a possible modulatory role for peripheral input in some FM patients. Across multiple independent investigations, nearly half of FM patients experienced clinically significant short-term pain relief following targeted peripheral blocks (45–58 percent). Two studies demonstrated statistically significant responder rates versus a 30 percent null ($p = 0.0232$ and $p = 0.0142$, respectively), reinforcing that a notable subset of patients derives immediate benefit from peripheral modulation. Even where p-values approached, but did not meet, the conventional $\alpha = 0.05$ threshold, the consistent direction and magnitude of effect point toward a clinically relevant phenomenon.

Mechanistically, these results support a model of dynamic interplay between peripheral inputs and central amplification. Peripheral signals, originating from small fiber pathology, neuroinflammation, or deep tissue metabolic changes, drive ongoing dorsal horn hyperexcitability, creating a sustained hyperalgesic state through neuroimmune and neuroendocrine feedback loops. The documented variability in patient responses indicates a heterogeneous FM population, emphasizing the need for personalized therapeutic strategies [5]. Intramuscular lidocaine injections at tender points resulted in response rates of approximately 45–46 percent [8,13].

Clinically, recognizing these peripheral phenotypes can guide targeted interventions. Diagnostic tools such as skin biopsy or CCM may identify patients most likely to benefit from peripheral-focused therapies (e.g., topical agents, nerve blocks, neuromodulation). Integrating these peripheral-directed approaches with centrally acting interventions (e.g., pharmacotherapy, cognitive behavioral therapy) and rehabilitation strategies may optimize outcomes.

Despite promising findings, several limitations constrain the interpretation of this synthesis and meta-analysis. First, heterogeneity in study populations, diagnostic criteria, and outcome measures complicates direct comparisons across studies. Some studies included mixed chronic pain cohorts or used outdated FM criteria, potentially inflating or underestimating responder rates and small fiber pathology prevalence.

Second, although the meta-analytic component incorporated published data, the number of studies with extractable quantitative metrics was limited. Statistical power is constrained by small sample sizes and the absence of individual participant data (IPD), precluding subgroup stratification or meta-regression. Funnel plot asymmetry could not be assessed due to the low number of studies, limiting evaluation of publication bias.

Third, the p-values reported, while statistically significant in some studies (e.g., $p = 0.0232$ and $p = 0.0142$), are based on dichotomous responder outcomes rather than continuous pain metrics. This binary classification may oversimplify nuanced clinical responses.

Finally, much of the evidence remains cross-sectional, limiting causal inference. While the correlation between small fiber pathology and symptom severity is robust, longitudinal studies are necessary to clarify whether peripheral abnormalities

precede, maintain, or result from central sensitization processes.

These limitations underscore the need for rigorously designed longitudinal trials with standardized endpoints, comprehensive peripheral and central assessments, and clearly defined FM phenotypes. Until such data are available, conclusions should be interpreted with appropriate caution.

Future research should emphasize longitudinal designs to elucidate temporal dynamics between peripheral and central sensitization processes. Omics-based biomarker exploration could enhance stratification, predicting therapeutic responses and informing precision medicine approaches.

Conclusion

Fibromyalgia pain amplification is driven primarily by central sensitization, yet accumulating evidence indicates that ongoing peripheral afferent signals, arising from discrete phenomena such as small fiber pathology, low-grade inflammation, or deep tissue metabolic derangements, can meaningfully sustain that sensitized state in a clinically relevant subset of patients. Approximately forty-nine percent of FM patients demonstrate small fiber pathology, and a subset of patients may achieve short-term pain relief from local anesthetic blocks, based on small, exploratory trials with limited generalizability. Together, these findings support a model in which roughly half of FM patients have a peripheral neuropathic component driving or augmenting their central sensitization. Future trials should test phenotype-guided strategies, combining peripheral nerve targeted blocks with centrally acting agents, to optimize outcomes for FM subgroups.

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Conflict of Interest

All the authors have read and approved the final version of the manuscript. All the authors declare no conflicts of interest.

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