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REVIEW

Small Fibre Pathology in Fibromyalgia: A review

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ABSTRACT

Fibromyalgia syndrome (FMS) presents a complex and challenging disorder in both the diagnosis and treatment, with emerging evidence suggesting a role of small fibre pathology (SFP) in its pathophysiology. The significance of the role of SFP in FMS remains unclear; however, recent evidence suggests degeneration and dysfunction of the peripheral nervous system, particularly small unmyelinated fibres, which may influence pathophysiology and underlying phenotype. Both skin biopsy and corneal confocal microscopy (CCM) have consistently demonstrated that ~ 50% of people with FMS have SFP. CCM, a non-invasive measure of small nerve fibres has detected small fibre loss, correlating with neuropathic pain descriptors. Additionally, quantitative sensory testing has shown abnormalities, primarily in pain pressure/mechanical pain thresholds. This narrative review provides a comprehensive understanding of the pathophysiological dimensions of FMS with a clear focus on small nerve fibres and the peripheral

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nervous system, offering a roadmap for future research.

Keywords: Fibromyalgia syndrome; Small nerve fibre; Small fibre pathology; Skin biopsy; Corneal confocal microscopy; Quantitative sensory testing

Key Points
Fibromyalgia syndrome is a complex and challenging disorder, with increasing evidence suggesting a possible role of the peripheral nervous system in its pathophysiology.
Studies have shown ~ 50% of patients with fibromyalgia have small fibre pathology, identified through skin biopsy or corneal confocal microscopy.
This narrative review provides an understanding of the pathophysiology of fibromyalgia syndrome with an emphasis on the role of small fibre pathology.
Both skin biopsy and corneal confocal microscopy are valuable tools for evaluating small fibre pathology in fibromyalgia.
Further mechanistic research on the pathophysiology of small fibre pathology, particularly in longitudinal cohort studies evaluating its natural history are required to improve the understanding of possible peripheral nervous pain-related mechanisms in fibromyalgia.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a highly prevalent but poorly understood condition. It results in chronic widespread pain (CWP), often accompanied by fatigue, cognitive impairment, sleep and mood disturbances [1], impacting on quality of life and social functioning [2]. This heterogeneous and complex syndrome can present major challenges in diagnosis, resulting in significant diagnostic delay and repeated investigations [3]. Consequently healthcare-related costs are substantial, while impaired work productivity incurs further indirect costs to both individuals and society [4, 5]. CWP is associated with excess mortality, explained primarily through increased cancer and cardiovascular mortality [6]. Despite the impact of FMS on the patient, the patient's family and society, no consistently effective treatments are available for negating pain or other symptoms, which is in part due to a lack of understanding of the patho-aetiology of FMS.

Primary FMS is characterised by its idiopathic nature, arising without any associated underlying disorder, while secondary FMS occurs in people with an underlying condition such as a rheumatological disease [7]. The prevalence of primary FMS is ~ 2–4% of the general population [8], although these epidemiological studies are primarily limited by heterogenous definitions [9]. In one UK study, the prevalence of fibromyalgia was 1.7% according to the 1990 criteria [10] (utilising tender point examination), 1.2% using the 2010 criteria [11] (clinician-determined, focused on the number of pain sites and other symptoms, without tender point exam), and 5.4% using modified 2010 criteria (self-reported symptoms) [12, 13]. Prevalence is similar across different countries although there are limited data on cultural variation; with little evidence of an increased prevalence in industrialised countries [14]. The prevalence of FMS increases with age, peaking at 50–60 years old [13] and is greater in women with a female-to-male ratio of 10:1, although epidemiological studies demonstrate ratios ranging from 2:1 to 30:1 depending on which American College of Rheumatology (ACR) fibromyalgia classification is used [8, 13]. FMS complicates other chronic diseases: the prevalence of secondary FMS is much higher in rheumatalogical diseases than in the general population, affecting around 18–24% of people with rheumatoid arthritis and 14–18% with spondyloarthritis [15].

For decades, the search for the pathogenic mechanism of fibromyalgia in the central

nervous system has been ongoing, until the paradigm shift to the peripheral nervous system occurred. The goal of this narrative review is to draw attention to the emerging evidence of the role of small fibre pathology (SFP) in FMS; however, uncertainty remains about the significance of its role.

METHODS

A comprehensive narrative review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles based on the authors' expertise. Articles published from inception of databases were identified. This review is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DIAGNOSTIC CRITERIA

FMS diagnostic criteria have evolved significantly over time. The first official diagnostic criteria were proposed by the ACR in 1990 and were based solely on the presence of chronic widespread pain and tender points in at least 11 of 18 specific sites [16]. In 2010, a newer version was proposed by the ACR, where 2 variables were identified to define FMS: the widespread pain index (WPI) and a symptom severity scale [16]. These criteria emphasize a comprehensive assessment of widespread pain, tenderness at specific points, and associated symptoms like fatigue and cognitive difficulties [16]. The shift acknowledges the complexity of FMS and aims for a more holistic understanding of its varied symptoms. Subjective self-reported measures and clinical examinations are commonly used in lieu of an objective diagnostic biomarker [17].

The pathophysiology of FMS is unknown, and the relative contribution of changes observed in the central (CNS) and the peripheral nervous system (PNS) are currently debated [18–20]. Traditionally, FMS has been considered a central pain-amplifying condition with central sensitisation and dysfunction of the descending pain-modulating system (DPMS), with, additionally, co-existing dysfunction of the hypothalamic–pituitary–adrenal axis and autonomic nervous system dysfunction with underpinning pain catastrophisation. However, more recently, a paradigm shift in the aetio-pathogenesis has been demonstrated. It is now clearly recognised that a subpopulation of people with FMS have abnormalities and dysfunction of the PNS, particularly of small unmyelinated (c) fibres [21]. It has been postulated that alterations within the CNS may occur in response to PNS degeneration and may occur as a result of neuroplasticity [22], in paradox to the historical concepts of the disorder. However, the directionality of the order of PNS and CNS alterations remain uncertain and requires further research. In this review, we will discuss the current understanding of the pathophysiology of FMS, with a focus on the PNS and small nerve fibre pathology and dysfunction.

PATHOPHYSIOLOGY

Genetic Factors

The role of genetics in FMS is poorly defined, but it is suggested that a genetically predisposed individual exposed to environmental stressors may develop FMS. The condition exhibits a strong familial aggregation, with first-degree relatives of patients with FMS being 8.5 times more likely to have the condition [1, 23]. Twin survey studies estimate heritability at 48–54%, and a genome-wide linkage scan in 116 families supports the heritability of FMS [24, 25].

Numerous pain-regulated genes, including those for catechol-O-methyltransferase, mu-opioid receptors, and voltage-gated sodium channels, have been identified [26]. Candidate-gene studies suggest a role for serotoninergic, dopaminergic, and catecholaminergic gene polymorphisms in FMS, although findings are inconsistent and not unique to FMS [27]. A large-scale comparative genomic study identified

significant differences in the genes, GABRB3, TAAR1, and GBP1, in people with FMS, potentially influencing nociception, inflammation, and mood. Understanding these gene polymorphisms may aid in better subclassifying people with FMS for more targeted pharmacological strategies [28–31].

CNS Alterations and Pain Mechanisms

The preponderance of data suggests that global grey matter volume remains unchanged in FMS [32, 33]. However, there are data to support an association between central sensitisation and decreased grey matter volume in specific brain regions with relevance for pain processing, including the anterior cingulate cortex, prefrontal cortex and insula [34, 35]. The association of these volumetric grey matter changes to measures of pain are weak, with confounding variables including co-existing affective disorders such as current major depressive episode, bipolar disorder, dysthymia, or general anxiety disorder [36].

Although there are only moderate-to-weak data on volumetric changes, there is stronger evidence of altered brain connectivity, particularly in multiple networks associated with spontaneous clinical pain [37, 38]. Studies of functional magnetic resonance imaging (fMRI), using resting state analysis, have documented alterations within the default mode network (DMN) [37, 39], along with increased connectivity between the somatosensory cortices and the DMN [40]. The DMN is a collection of brain regions involved in self-referential thinking, and it deactivates when attention is directed externally toward sensory processes or task conditions [41]. Altered brain connectivity between the insula cortex and the DMN, along with altered connectivity between pain-processing structures such as the anterior cingulate cortex and insula cortex, have also been reported [37, 42, 43]. Alterations in the DMN are associated with chronic pain conditions. However, Ceko et al. [44], investigating the effects of lived chronic pain and current experienced clinical pain (also known as the experienced pain by the patient during the fMRI scan or ongoing pain), demonstrated that currently pain-free patients with FMS demonstrated similar DMN resting-state connectivity to healthy control subjects. People with FMS experiencing current clinical pain at the time of scanning had significantly increased DMN connectivity to the bilateral anterior insula, which showed a positive correlation with the level of their current pain [44]. The study proposes that temporary interruptions in the DMN caused by the immediate clinical pain experienced during scanning (ongoing pain) may contribute to the disruptions in DMN connectivity observed in chronic pain [44].

FMS is associated with altered functional connectivity within the limbic system. Lower resting state functional connectivity has been demonstrated in the medial hypothalamus, thalamus and amygdala compared to healthy people [45]. As part of the hypothalamic–pituitary–adrenal axis, alterations in hypothalamic activation leads to increased inflammation and stress responses, both frequently reported in patients with FMS [19, 20]. Additionally, neurotransmitter abnormalities, including decreased dopamine availability and increased glutamate levels in the anterior cingulate cortex, amygdala and hippocampus, are associated with pain in FMS [46, 47].

Temporal summation is a pain phenotyping method in which repeated application of identical nociceptive stimuli can be used to detect the presence of central sensitisation. People with FMS report greater pain scores in response to supra-pain thresholds and repetitive noxious stimuli [48–51]. Staud et al. [52] assessed spinal cord neural activation and functional connectivity within brainstem nuclei during a temporal summation of pain paradigm, and utilised it to model the observed blood-oxygen-level-dependent (BOLD) time-course with pain ratings. The study found similar patterns of spinal activity in FMS and healthy participants; however, higher BOLD brainstem activity was associated in people with FMS [48]. These findings lend additional support to the presence of alterations to pain modulation. Dysfunction of the DPMS is well documented in FMS [53–55]. The DPMS comprises a network of widely distributed brain regions whose integration is essential for

modulating sensory input to the central nervous system and behavioural responses to pain [56]. However, the underlying mechanisms of this dysregulation in FMS are poorly understood. The conditioned pain modulation test is an experimental measure of the function of the DPMS based on the 'pain-suppress-pain' phenomenon, and has been shown to elicit widespread reductions in connectivity of regions engaged in nociceptive processing such as the thalamus, insula, and secondary somatosensory cortex [57]. Attenuation of these modulatory pathways is associated with increased connectivity between the insula and the default-mode network and decreased connectivity between the default-mode network and other pain-inhibitory regions [58].

In 2017, The International Association for the Study of Pain introduced the term 'nociplastic pain' as a third type of classification of pain, in addition to nociceptive and neuropathic pain. It is referred to as pain arising from altered nociception without clear evidence of tissue damage. It is prevalent in conditions like FMS, which proposes a possible relevance as an endophenotype reflecting central sensitisation. Although, in nociplastic pain conditions, central sensitization is most likely a dominating mechanism, a contribution of peripheral sensitization cannot be excluded [59]. Central sensitisation is described as hyperexcitability of the central nervous system and increased responsiveness to a variety of stimuli, including temperature, pressure, and medication [32], leading to widespread pain, while peripheral sensitisation is the change in the sensitivity of sensory fibres leading to the reduction in the threshold of nociceptive afferent receptors initiated by tissue damage [60].

Although there have been many studies documenting alterations in the CNS, they have not provided evidence of a direct causal role of pain in FMS. However, there is growing evidence supporting the presence of SFP in a proportion of patients with FMS [18, 61–64]. Alterations in the CNS have been demonstrated in other pain disorders which are primarily of a peripheral nerve origin. For instance, grey matter alterations in the anterior cingulate cortex and pre-frontal cortex together with alterations in functional connectivity have been clearly described in painful diabetic peripheral neuropathy [65–67]. This proposes that possibly the pathomechanisms of the central changes, observed in FMS, could be of a secondary nature (neuroplasticity) occurring in part as a response to peripheral nerve degeneration [68]. However, the causality or specificity of PNS changes as the sole driver of CNS changes has not been established, given the lack of natural history studies. Additionally, a different opinion was published by Clauw, suggesting that small nerve fibres changes could be secondary to central alterations, proving that further research is required to have a better understanding on this topic [69].

In a prospective case–control study which included 43 women diagnosed with FMS syndrome (meeting the diagnostic criteria according to the 2010 ACR guidelines) and 40 healthy controls, participants were further stratified into subgroups based on reduced (n = 21) or normal (n = 22) skin innervation [11, 70]. The subgroup with reduced skin innervation demonstrated hyperconnectivity between the inferior frontal gyrus, the angular gyrus and the posterior parietal gyrus. These results suggest pronounced pathology in the peripheral nervous system and demonstrate alterations in morphology, structure and functional connectivity at the level of the encephalon [70].

Role of Small Fibre Pathology

The mechanisms that lead to small fibre dysfunction, and, indeed, the pathophysiological role of these abnormalities, remain a matter of debate. In various clinical contexts, alterations occur within small nerve fibres, distinct from the typical manifestations of small fibre neuropathy (SFN) [71]. The changes in FMS are termed as SFP given its debated role in patho-mechanisms. Similarly, small nerve fibre alterations and reduction in nerve densities have been observed in other conditions, such as Parkinson's disease and amyotrophic lateral sclerosis [72]. However, in FMS, a condition primarily marked by widespread and debilitating pain, these small fibre alterations may hold a major pathophysiological role [73].

Our meta-analysis reported the prevalence of SFP in FMS to be approaching 50% [62]. FMS shares sensory symptom overlap with conditions that primarily originate from the PNS, including painful diabetic neuropathy [74], as evidenced by a loss of function in thermal pain discrimination [75–79]. SFP can induce hyperexcitability resulting in spontaneously active or sensitised sensory neurons. This patho-mechanism may contribute to spontaneous pain, hyperalgesia and allodynia. Hyperexcitability in c fibre nociceptors have been recognised in fibromyalgia. Microneurography studies by Serra and Evdokimov et al. have identified abnormal spontaneous activity in 'silent c nociceptors' in a large proportion of individuals with FMS [80, 81]. These nerve fibres are normally insensitive to mechanical or thermal stimuli but become sensitised in pathological conditions. Both studies also demonstrated increased mechanical sensitisation in mechanosensitive c nociceptors in patients with FMS, similar to that seen in patients with cryptogenic/idiopathic small fibre neuropathy (ISFN) [80, 81]. However, no sensitisation to thermal stimuli was seen. Compared to patients with ISFN, FMS displayed greater slowing of conduction velocity in silent c-nociceptors which has been hypothesised to occur due to axonopathy [81]. These findings were subsequently confirmed by Doppler et al. using electron microscopy of dermal nerves obtained using skin biopsy from the proximal and distal leg and index finger. The diameter of unmyelinated dermal axons was reduced at all sites compared to healthy participants and in the proximal leg and index finger compared to patients with ISFN [61].

Moreover, a study by Jänsch et al. discussed if FMS equals SFN, the study directly compared 158 women with FMS and 53 with SFN. SFP was present in 69.7% of patients with FMS and 73.6% of patients with SFN [93]. Patients with FMS were younger (~ 10 years) at symptom onset, described higher pain intensities requiring frequent change of pharmaceutics, and reported generalised pain compared to SFN [99]. Patients with FMS demonstrated reduced skin innervation proximally and higher corneal nerve branch densities ($P < 0.001$) whereas patients with SFN were characterised by reduced cold detection and prolonged electrical A-delta conduction latencies ($P < 0.05$) [99].

Ion channels, Genes and Nuerotransmitters

The excitability of sensory nerves is driven by ion channels and axonal membrane potentials. The distinctive expression of various ion channels within subtypes of sensory neurons delineates their specific roles in pain signalling. For instance, voltage-gated sodium channels, such as Nav1.7 and Nav1.8, play crucial roles in initiating and propagating pain signals, highlighting the significance of ion channel diversity in modulating pain perception [82]. Additionally, the expression of specific transient receptor potential (TRP) channels, like TRPV1 and TRPM8, contributes to the detection of thermal stimuli, further illustrating the nuanced involvement of ion channels in the complex landscape of pain sensation [83]. Examples of rare genetic mutations illustrate either extreme pain phenotypes or pain insensitivity [84]. For example, gain-of-function mutations in SCN9A, which encodes the highly expressed voltage-gated sodium channel Nav1.7 in peripheral nociceptive fibres, result in chronic pain disorders such as inherited erythromelalgia [85] and paroxysmal extreme pain disorder [85]. In contrast, the loss of function of SCN9A results in congenital insensitivity to pain [86]. Gain-of-function variants of genes that encode voltage-gated sodium channels have been proposed to play a role in both widespread muscle pain syndromes [87, 88], neuropathic pain disorders [89] and SCN9A gene-encoded Nav1.7 dorsal root ganglia sodium channel variants in severe FMS phenotypes [90]. In a retrospective study by Eijkenboom et al., 1139 patients diagnosed with pure SFN were screened for SCN9A, SCN10A and SCN11A variants, and 11.6% (132) of the patients were shown to have pathogenic VGSC variants, which demonstrates a putative association between pathogenic voltage-gated sodium channels variants and SFN [91].

Furthermore, Martinez-Lavin et al. hypothesised that enhanced dorsal root ganglion (DRG) excitability may play a key role in FMS pain [92]. DRG can play a central role in pain FMS through psychological stress, physical trauma

and auto-immunity [93]. DRG has valuable role in the pathophysiology of neuropathic pain, through pronociceptive ion channels including voltage activated sodium channels, calcium channels and transient receptor potential channels. In addition, DRG nuclear degeneration can also explain peripheral denervation found in SFN. The damaged nuclei can result in distal nerve atrophy being unable to maintain the metabolic needs of the nerve unit [94].

A study by Ślęczkowska et al. [95] investigated the role of 15 ion channels in neuropathic pain among patients with SFN, where 4.8% of individuals had potentially pathogenic heterozygous variants in ion-channel genes. The most frequently affected genes were TRP genes, including TRPA1, TRPM8, TRPV1, and TRPV3. Patients with ion-channel gene variants reported more severe pain, emphasising the significance of these genetic factors in neuropathic pain across various aetiologies [95].

A study of male Sprague–Dawley rats showed decreased intra-epidermal nerve fibre density (IENFD) occurred in response to the increased levels of glutamate in the insular cortex (through the administration of a glutamate inhibitor) [69]. Whilst this suggests that pro-nociceptive changes within the central nervous system may result in downstream post-synaptic small fibre degeneration. However, mechanisms that may lead to these alterations are yet to be elucidated. Indeed, recent evidence directly links auto-immune mechanisms to abnormal structure and function of primary afferent fibres. Passive transfer of serum from patients with FMS to mice resulted in thermal and pressure hyperalgesia, nociceptor hyperexcitability and binding of IgG to satellite glial cells in the DRG, with a modest reduction in IENFD [96]. Thus, providing evidence of an auto-antibody-mediated pathway leading to small fibre degeneration, accompanied by a reduction in IENFD.

A study by Gerdle et al. [97] investigated the presence of peripheral metabolic and algesic muscle alterations in women with FMS through microdialysis, revealing increased concentrations of glutamate, pyruvate, and lactate. Following a 15-week exercise intervention, significant reductions in pain intensity and metabolic markers were observed, supporting the notion that exercise partially normalizes peripheral factors contributing to pain in patients with FMS [97]. Supervised regular physical activity demonstrated significant improvement in the Fibromyalgia Impact Questionnaire (FIQ) and IENFD at proximal and distal sites [98].

MEASURE OF SMALL NERVE FIBRES AND NERVE FUNCTION

Skin Biopsy

Skin punch biopsy is a minimally invasive technique which provides a reliable method of interrogating the skin's innervation status through analysis of dermal and intraepidermal nerve fibres (IENF). IENF are the terminal endings of nociceptive unmyelinated c fibres and myelinated Aδ fibres and innervate the epidermis carrying sensory information pertaining to temperature and pain from the periphery to the dorsal root ganglia and then to the CNS. Studying the morphometry and densities of IENFs provides an insight into the pathology of the PNS.

Over the past two decades, the skin punch biopsy has been established as the de facto reference technique for investigators studying small nerve fibres (and SFN) [100, 101]. Indeed, guidelines on the use of punch biopsies have been developed by the European Federation of Neurological Societies/Peripheral Nerve Society joint task force [101]. Such guidance recommends the visualisation of dermal nerve fibres and IENFs using protein gene product 9.5 (PGP 9.5), a ubiquitous pan-axonal marker which provides unequivocal staining of dermal and epidermal nerve fibres [102].

Briefly, 3-mm punch biopsies are taken from the skin of the distal leg, lower thigh or upper thigh (sites of normative reference values) before being fixed, frozen, and sectioned at 50-µm thickness. Sections are stained with PGP 9.5 for visualisation via bright-field microscopy (Fig. 1). Internationally validated methods are then employed to identify/count nerves crossing the dermal–epidermal junction, providing

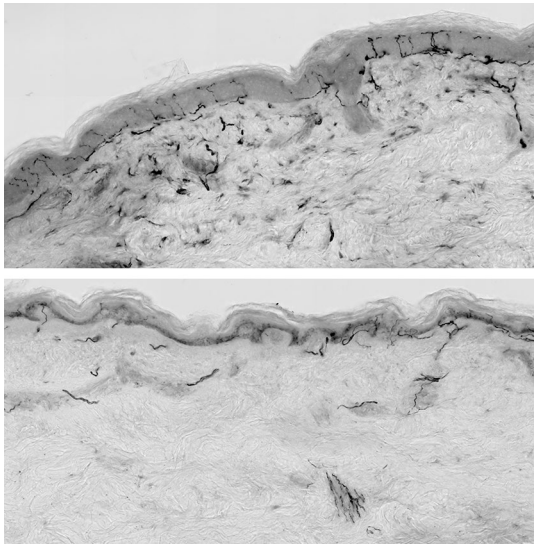

Fig. 1 Examples of skin biopsy images from healthy individuals (*top*) and people with fibromyalgia syndrome (FMS) (*bottom*); note reduction in the number of intraepidermal nerve fibres in the images from individuals with FMS (*bottom*). Original images

a measure of IENF density (IENFD; IENF/mm) which can then be compared with normative reference ranges [103].

As previously discussed, a subset of people with FMS have a reduced IENFD indicative of a SFP [18, 61, 79, 81, 104–106] Table 1 lists some studies evaluating SFP in FMS. In 2015, Levine et al. [17] postulated that the skin punch biopsy may be of benefit in detecting SFP in FMS [17]. Indeed, our meta-analysis of eight studies found the prevalence of SFP in patients with FMS to be 49% (95% CI 38–60%) [62]. Whilst previous studies have reported findings primarily from females with FMS, a recent study in men with FMS also indicates a high prevalence of SPF (83%). Furthermore, more than 50% of men with FMS had a generalised reduction in IENFD compared to 15% in females [81, 149]. Importantly, it has been demonstrated that patients with FMS with reductions in IEFND have a more debilitating (greater pain) FMS phenotype [81]. The extent of SFP may relate to the severity of FMS symptomology; however, this hypothesis remains contentious. We have recently published a large skin biopsy study in FMS and ISFN, which again consistently demonstrated a reduction in IENFD when compared with healthy volunteers [107].

There are several putative pain-related mechanisms of small nerve fibres in FMS. The heightened sensitivity of nociceptive c fibres and their associated Schwann cells in individuals with FMS is associated with unmyelinated free nerve endings in the epidermis, as observed through bright-field and electron imaging [117, 118]. Notably, increased inflammatory cytokines, oxidative stress and mitochondrial dysfunction have been identified in skin biopsies of people with FMS [119, 120]. Furthermore, a subset of people with FMS also exhibited a non-length-dependent SFP which correlated with the presence of trisulfate heparin disaccharide antibodies within participants' skin biopsy [121]. Skin biopsies have also demonstrated that patients with FMS have increased expression of NMDA receptors compared to healthy controls [122]. Immunofluorescence microscopy also has a wide application in the analysis of skin biopsies, and normative values for IENFD by immunofluorescence microscopy have been published [123]. Immunofluorescence microscopy was utilised by both Falco et al. [109] and Leone et al. [110].

To date, there has been one longitudinal study of skin biopsy in FMS. Sixty-two patients with FMS were evaluated with skin biopsy and clinical assessment and after 18 months; overall, IENFD remained unchanged while those that did demonstrate a reduced IENFD at proximal and distal sites, together with fatigue and BPI-motor and work sub-scores, were predictors of more severe disability measured with the FIQ [111]. It has been thus hypothesised that small fibre dysfunction on motor performance could have a role in the evolution of FMS.

Corneal Confocal Microscopy

The cornea is the most densely innervated tissue of the human body and receives sensory innervation from the ophthalmic branches of the trigeminal ganglion [124]. CCM is a non-invasive, reiterative and rapid method to image these nerves at ×600 magnification to be used as a marker of small nerve fibre deficits in a range of peripheral neuropathies (Fig. 2) [125].

Table 1 Table of major studies of SFP in FMS

Author	Year	Country	Sample size	FMS (% of cohort)	Gender (% women/female patients in FMS group)	SFP found (% of FMS group)	Modality of measuring SFP
Marshall et al. [108]	2024	UK	40	75	93	50	CCM
Falco et al. [109]	2024	Italy	138	42	90	40	Skin biopsy
Jänsch et al. [99]	2024	Germany	211	75	100	70	Skin biopsy and QST
Leone et al. [110]	2023	Italy	94	68	94	31	Skin biopsy
Quitadamo et al. [111]	2023	Italy	62	100	94	84	Skin biopsy
Boneparth et al. [112]	2022	USA	38	39	93	53	Skin biopsy
Vecchio et al. [113]	2020	Italy	81	100	–	85	Skin biopsy
Fasolino et al. [114]	2020	Italy	57	100	95	32	Skin biopsy
Evdokimov et al. [81]	2019	Germany	117	100	100	63	Skin biopsy
Lawson et al. [115]	2018	USA	155	100	68	40	Skin biopsy
Leinders et al. [116]	2016	Germany	30	100	93	50	Skin biopsy
Oudejans et al. [63]	2015	Netherlands	39	100	92	51	CCM
Ramírez et al. [64]	2015	Mexico	34	50	100	71	CCM
de Tommaso et al. [20]	2014	Italy	81	26	86	76	Skin biopsy
Giannoccaro et al. [105]	2014	Italy	20	100	95	30	Skin biopsy
Kosmidis et al. [104]	2014	Greece	80	58	89	34	Skin biopsy
Üçeyler et al. [79]	2013	Germany	90	28	92	42	Skin biopsy and QST
Oaklander et al. [18]	2013	USA	57	47	74	41	Skin biopsy
Fuelner et al. [149]	2024	Germany	59	71	0	83	Skin biopsy

CCM corneal confocal microscopy, *FMS* fibromyalgia syndrome, *QST* qualitative sensory testing, *SFP* small fibre pathology

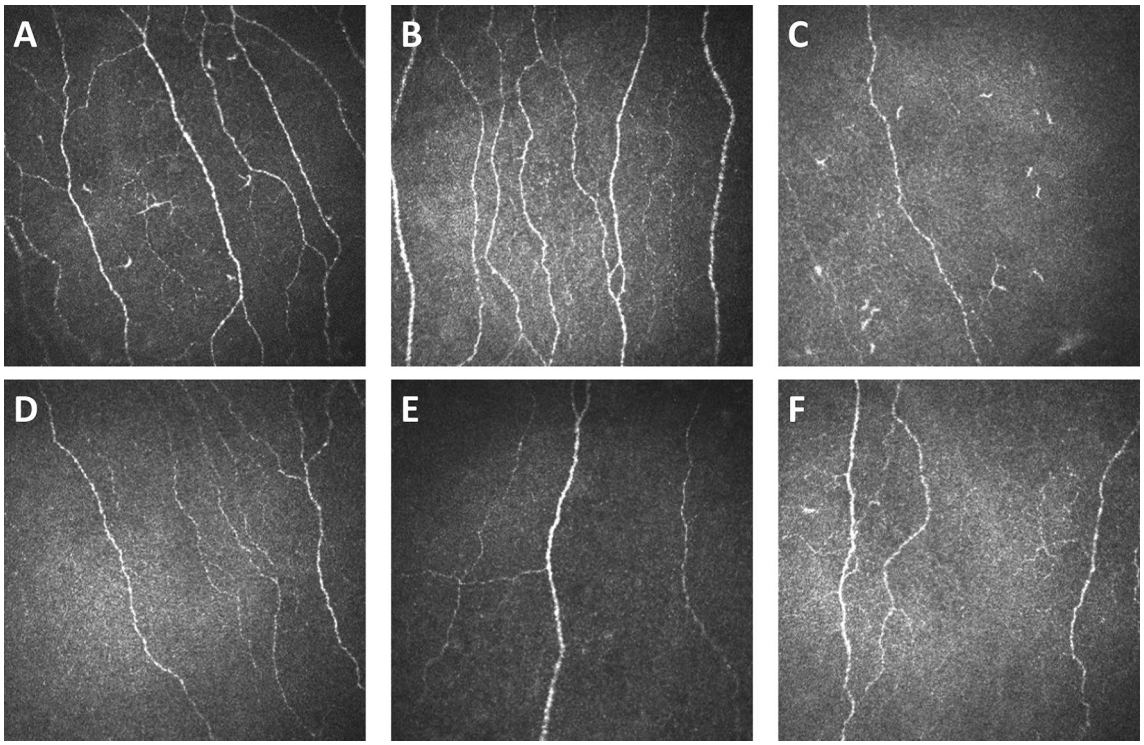

Fig. 2 Examples of CCM images from healthy individuals (**A**, **B**) and people with SFP and FMS (**C**–**F**); note reduction in the number of corneal nerves and number of branching nerves in the images from individuals with SFP and FMS (**C**–**F**). Original images

A reduction in small nerve fibres has been confirmed by alterations in corneal sub-basal plexus density in people with FMS [64, 126–128]. Corneal nerve fibre loss has been associated with neuropathic pain descriptors selected in FMS (Fig. 2) [64]. Indeed, sub-basal corneal morphometry share a negative correlation with the WPI [129]. Furthermore, reductions in sub-basal plexus nerve density and length correlated with ocular and visual symptoms in FMS [127, 128]. Higher corneal sensibility thresholds have been identified in FMS, in addition to a negative correlation of the Schirmer test with the WPI and corneal nerve fibre density [129–131]. However, no significant correlation has been observed between corneal morphometry and screening instruments (painDETECT, Small Fibre Neuropathy Screening List) or functional measures such as quantitative sensory testing (QST) [126]. More importantly, loss of sub-basal nerve fibres correlated in parallel with reductions of IENF in both proximal and distal leg and upper thigh skin biopsies taken from people with FMS [81]. Our recent study confirmed that SFP is present in a proportion of people with (again ~ 50%). We also demonstrated that, in a proportion of people with FMS, symptoms compatible with SFN were present in the absence of structural SFP with greater mechanical pain sensitivity, depression and anxiety seen within the same group [108]. In another recent study, we demonstrated that participants with SFP, in both FMS and idiopathic distal sensory polyneuropathy, reported symptoms indicative of small nerve fibre disease albeit with differing distinctions in pain distributions [132].

Quantitative Sensory Testing (QST)

QST encompasses an assessment of the full spectrum of primary afferent nerve fibres and pathways, enabling quantification of the associated somatosensory function [133]. QST provides

valuable information on large and small nerve fibre functionality in neuropathic pain [134]. Many studies in FMS have incorporated QST into their assessment protocol, initially focussed on testing thermal detection, thermal pain and pressure pain thresholds (PPTs) [75, 135–137]. Comparison across studies has proved difficult due to disparate data collection methods and variation of body sites tested (Table 1). However, across the majority of studies, people with FMS have demonstrated dysfunction of thermal detection and thermal pain thresholds along with increased sensitivity to pressure pain [33, 137].

A standardised QST protocol was developed by The German Research Network on Neuropathic Pain (DFNS) in 2006, along with normative data for age, gender, and test site, which allowed for easier comparison of results across multiple studies [138]. Early studies following the introduction of the DFNS standardised protocol demonstrated thermal detection thresholds within the normative range with no significant difference between people with FMS and healthy volunteers [135, 139]. Subsequent studies have identified dysfunction of thermal detection, but not consistently across studies: Üçeyler et al. showed increased cold and warm detection thresholds (thermal hypoesthesia) [79], Gerhardt et al. demonstrated warm detection hyperesthesia [140] and Evdokimov et al. warm but not cold hypoesthesia, compared to healthy volunteers [81]. Thermal pain detection findings are overall more consistent. Most QST studies now report cold hyperalgesia as a significant finding in FMS, whether this is accompanied by warm hyperalgesia and whether these are body site-specific (e.g. painful body area vs. no pain body area vs. generalised) is more variable [81, 139–141]. Increased pressure pain sensitivity (pressure hyperalgesia) is consistently demonstrated when compared to healthy participants or other pain conditions. Increased mechanical detection thresholds along with a gain of function in mechanical pain sensitivity are common findings [142].

The diversity in QST results, coupled with inconsistent observations of small fibre degeneration in IENFD and CCM parameters, suggests the presence of distinct subgroups among patients with FMS. These subgroups have exhibited varying degrees of SFP, neuropathy symptoms, and central involvement [113, 143]. Using mean QST values in studies may overlook these nuanced findings.

Recent studies have categorised patients based on the presence or absence of SFP, determined through IENFD or a comparison of reported pain symptoms. Kaziyama et al. stratified patients with FMS into asymmetrical and symmetrical pain cohorts. IENFD did not differ between each side of the body in people with asymmetrical symptoms or between people with asymmetrical and symmetrical symptoms. However, a comparison of QST in the patients with asymmetrical symptoms revealed that the PPT was significantly reduced on the painful side, with values similar to those of the symmetrical cohort.

Fasolino et al. [114] assessed 57 patients with fibromyalgia, of which approximately one-third had confirmed SFP by measuring IENFD at the distal leg. Patients with SFP had equivalent IENFD at proximal and distal sites, confirming non-length-dependent pathology. QST demonstrated no significant difference between the sensory profiles of patients with and without SFP, with the majority of mean scores falling within the normative range. However, mechanical pain sensitivity exhibited a significant gain of function, in keeping with sensitisation along mechano-nociceptor pathways, but showed no significant difference between those with and without SFP.

Dysautonomia

Previous studies have proposed FMS as a dysautonomia-related pain syndrome [127, 144], with increased tonic sympathetic activity. Fatigue and widespread pain may be secondary to peripheral tissue ischemia produced by excessive vascular tone, due to sympathetically mediated vasoconstriction [145]. Heart rate variability studies in FMS (a measure of the cardiac autonomic function) have demonstrated alterations consistent with sympathetic hyperactivity and associated sympathetic hypo-reactivity to orthostatic stress [146]. However, a recent study showed reduced skin conductance and

reduced reactivity to a physiological manipulation, such as anxiety and body temperature, suggesting reduced sympathetic activity to the skin [147] and a loss of functionality (rather than gain of function) of the autonomic nervous system. Ramírez et al. evaluated the correlation between corneal nerve density and small fibre symptoms in women with FMS and subdivided them into those with and without severe anxiety or depression [148]. Corneal denervation was comparable in both cohorts. However, individuals with severe anxiety or depression exhibited heightened symptoms of SFN and dysautonomia. Among patients without severe anxiety or depression, a significant negative correlation was observed between corneal innervation and symptoms of dysautonomia and neuropathy. The absence of this correlation in individuals with severe anxiety or depression suggests a potential distortion in symptom perception. This distortion could, in part, elucidate the observed lack of structural and functional relationships seen in numerous prior studies.

CONCLUSION

SFP occurs in ~ 50% of people using skin biopsy or CCM. The latter has emerged as a valuable tool for assessing SFP in FMS given its non-invasive, reiterative nature. Further research is required on the pathophysiology of SFP in FMS and is essential to determine the timing, natural history, neuroplasticity and heterogeneity to improve our overall understanding of how PNS may contribute to pain in FMS.

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Declarations

Conflict of interest. Anne Marshall, Mohamed Elshafei, Frank G Preston, Jamie Burgess, Nicola Goodson, Nicholas Fallon, Bernhard Frank, Sizheng Steven Zhao declare no relevant conflicts of interest. Uazman Alam has no relevant conflicts of interests pertaining to this manuscript but declares that he has received honoraria from Viatris, Grünenthal, Eli Lilly, Procter & Gamble for educational meetings and has received investigator-led funding form Proctor & Gamble. Uazman Alam has also received sponsorship to attend educational meetings from Daiichi Sankyo and Sanofi.

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