Observational Study

Pressure-Induced Referred Pain as a Biomarker of Pain Sensitivity in Fibromyalgia

Rubén Arroyo-Fernández, MS[1,2,4], Elisabeth Bravo-Esteban, PhD[2,4], Víctor Doménech-García, MS[3], and Asunción Ferri-Morales, PhD[2,5]

From: [1]Physiotherapy Unit, Nª Sª del Prado Hospital, Talavera de la Reina, Spain; [2]University of Castilla-La Mancha, Faculty of Physiotherapy and Nursing, Toledo, Spain; [3]Universidad San Jorge, Zaragoza, Spain; [4]Toledo Physiotherapy Research Group (GIFTO); [5]University of Castilla-La Mancha, Health and Social Research Center, Cuenca, Spain

Address Correspondence:
Elizabeth Bravo Esteban-Herreros, PhD
Faculty of Physiotherapy and Nursing
Castilla–La Mancha University
Avda. Carlos III, s/n
45071 Toledo, Spain
E-mail:
Elizabeth.Bravo@uclm.es

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Background: Fibromyalgia (FM) syndrome is characterized by widespread pain, fatigue, and generalized increased pain sensitivity. Appropriate and simple pain models are methods employed to assess pain mechanisms that can potentially lead to improved treatments. Pressure pain thresholds (PPTs) or mapping the referred pain area produced by pressure stimulation at suprathreshold intensities are used to assess pain mechanisms. The optimal suprathreshold stimulation intensity to elicit referred pain with minimal discomfort for patients with FM has yet to be determined.

Objectives: The aim of this study was to compare the area and intensity of pressure-induced referred pain in patients with FM as elicited by systematic increases in PPTs, compared with controls.

Study Design: Observational, crossed-section study.

Setting: Research laboratory.

Methods: Twenty-six patients with FM and 26 healthy controls, age- and gender-matched, were included. Suprathreshold stimulation was applied to the infraspinatus muscle of the dominant side at 4 different intensities (PPT +20%, +30%, +40%, and +50%), after which referred pain was evaluated by measuring the area of pain in pixels using a digital body chart and its intensity on a Visual Analog Scale. Factors related to anxiety condition, pain catastrophizing, depression, and quality of life were recorded.

Results: The referred pain areas were larger in the FM group compared with healthy individuals at 120% ($P = 0.024$), 130% ($P = 0.001$), 140% ($P = 0.001$), and 150% ($P = 0.001$) PPT, however, within the FM group no differences were found between the intensity of suprathreshold stimulation and the size of the referred pain areas ($P = 0.135$) or pain intensity ($P > 0.05$). There was a positive correlation between the size of referred pain areas and pain catastrophizing in the FM group ($r = 0.457$, $P = 0.032$).

Limitations: This study presents some limitations, among which is the variability found in the referred pain areas.

Conclusions: These findings show that referred pain induced by applying a suprathreshold pressure of 120% PPT can be a useful biomarker to assess sensitized pain mechanisms in patients suffering from FM.

Key words: Referred pain, pain sensitivity, fibromyalgia, central sensitization, suprathreshold, pressure pain threshold, biomarker, facilitated pain mechanisms

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Fibromyalgia (FM) syndrome is a chronic, painful, noninflammatory rheumatic disease with high negative impact on quality of life (1,2). FM is characterized by widespread pain, fatigue, and generalized increased pain sensitivity on examination (3), the first of which is critical for its diagnosis (4-6), as well as psychological components, such as depression, pain catastrophizing, or kinesiophobia (7,8). Central sensitization (CS) is believed to be the common underlying mechanism to increased pain sensitivity and widespread areas of pain (9). For this reason, some authors (10-13) tend to employ terms, such as "sensitized central pain mechanisms" or "facilitated pain mechanisms," instead of "central sensitization" to refer to facilitated pain responses in humans.

Although FM symptoms can be explained within the theoretic framework of CS, to date, there are no assessment methods available to directly measure the activity of dorsal horn nociceptive neurons in humans. Nevertheless, surrogate pain models have been extensively used in research investigating facilitated pain mechanisms in patients with FM, as well as in other chronic pain conditions. Appropriate and simple pain models are methods employed to assess pain mechanisms that can potentially lead to improved treatments (14,15), as is the case for pressure pain thresholds (PPTs), which have been widely investigated in several diseases (16-26). These studies reported the presence of generalized increased sensitivity to pressure pain as an indicator of sensitized pain mechanisms. However, it has been suggested that PPTs might not be as useful as stimulation at suprathreshold intensities to assess pain mechanisms (27-29).

Previous studies have used PPTs combined with mapping the referred pain area produced by pressure stimulation at suprathreshold intensities to assess pain mechanisms (30). An expansion in the referred pain area, as assessed in somatic structures, may reflect increased sensitivity of pain mechanisms (21,31). Interestingly, it has been suggested that the expansion of local pain and referred pain may share common mechanisms and be part of the same phenomenon (15). For these reasons, mapping of both local and referred pain has been singled out as a potential sensitive biomarker for pain mechanisms (31). To induce referred pain in a noninvasive manner, former studies have used intensities for pressure stimulation of 20% (31) and 30% (32) above the PPT by applying a tonic, nociceptive pressure stimulus on somatic structures. However, whether these findings apply for clinical populations that may be more sensitive to high-pressure stimuli, such as those with FM syndrome, have not been tested. Moreover, the optimal stimulation intensity to elicit referred pain with minimal discomfort for patients has yet to be determined.

The objective of this study was to compare the area and intensity of pressure-induced referred pain in patients with FM as elicited by systematic increases in PPT compared with controls. The hypotheses were that patients with FM (1) would not elicit stepwise increases in the area of referred pain when suprathreshold pressure intensities were increased; (2) would experience increased pressure pain sensitivity; and (3) would report greater areas of referred pain elicited by suprathreshold pressure stimulation.

Methods

Patients

Patients diagnosed with FM syndrome were recruited from a local association (FM group, n = 26), and age- and gender-matched healthy patients were included as a control (control group, n = 26). The inclusion criteria for the FM group were being diagnosed with FM syndrome in accordance with the criteria by the American College of Rheumatology (33), being older than 18 years of age, and properly understanding spoken and written Spanish. Criteria for exclusion were being diagnosed with a psychiatric disorder or suffering from a noncontrolled rheumatic pathology. The selection criteria to be met by the control group were the same with the exception of being diagnosed with FM. Patients were provided with detailed information about the protocol and signed informed consent before being enrolled. The intervention took place between August 20th and September 25th of 2019. The study was performed in accordance with the Declaration of Helsinki, was approved by the local ethics committee (14/2017), and was registered at ClinicalTrials.gov (NCT04047407). The study was conducted in accordance with the STROBE statement for observational studies in epidemiology.

Protocol

We performed an observational, crossed-section study conducted in a single session. The following data were recorded: anthropometric (height, weight, and body mass index), sociodemographic (age and gender), and clinical-psychological [years since diagnosis, anxiety condition (34), pain catastrophizing (35), depression (36), and quality of life (37)]. Subsequently, the PPT was

measured bilaterally at the supraspinatus, infraspinatus, lower trapezius, and gastrocnemius muscles. After a 5-minute rest, the referred pain was evaluated by stimulating the infraspinatus muscle of the dominant side using suprathreshold pressure at the same location where the PPT was established. The suprathreshold pressure stimulation was applied at 4 different stimulation intensities (PPT +20%, +30%, +40%, and +50%) that were randomly administered in an ascending or descending order. The complete protocol was conducted with the patient in prone position.

Pain Sensitivity

To record the PPT bilaterally, a manual pressure algometer (Force Ten; Wagner Instruments, Riverside, CT) with a 1-cm^2 probe was employed at 4 points (38): (1) supraspinatus muscle (1 cm cranial halfway at the spine of the scapula); (2) infraspinatus muscle (intermediate point between the inferior angle of the scapula, the spine of the scapula, and medial angle of the scapula); (3) lower trapezius muscle (4–5 cm lateral to the apophysis of the spine at the seventh thoracic vertebra); and (4) gastrocnemius muscle (one-third distal to the medial gastrocnemius muscle). Pressure was raised until the patient indicated verbally that the feeling of pressure had become painful. This process was repeated 3 times with a minimum pause of 30 seconds between applications and the mean was calculated for posterior analysis. The value of each PPT was estimated in kg/cm^2.

Pressure-Induced Referred Pain

Suprathreshold pressure stimulation was applied to the infraspinatus muscle of the dominant side at the location where the PPT was established using the same algometer. All patients received suprathreshold pressure stimulation at 4 different intensities: PPT +20% (120% PPT), +30% (130% PPT), +40% (140% PPT), and +50% (150% PPT), each lasting 60 seconds and with a minimum break of 5 minutes between stimulations to reestablish a normal response from the central nervous system (38). Stimuli were randomly applied in an ascending (from lower to higher intensity) or descending (from higher to lower intensity) order. After each stimulation, each patient was requested to mark the area in pain on a digital tablet using an application with a digitalized body chart (Navigate Pain; Aalborg University, Aalborg, Denmark) (39). Using digitalized drawings in tablets to mark areas in pain has been shown to be a valid and reliable method to assess these body regions, being comparable to paper records (40). The size of referred pain areas indicated by each patient was estimated in pixels.

The body chart was subdivided into 15 different regions (Fig. 1) (31,38): (1) the posterior head and neck area from the occipital process at the top to the cervicothoracic junction at the bottom; (2) supraspinal area, limited by the base of the neck at C7 and the spine of the scapula; (3) pressure site area, overlying the infraspinatus area; (4) posterior shoulder, corresponding to the posterior deltoid muscle; (5) the back area, comprising the ipsilateral part of the thoracic and lumbar spine below the infraspinatus area; (6) the posterior arm, namely the area between the posterior deltoid and the line joining the lateral and the medial epicondyles at the elbow; (7) the posterior forearm area, limited proximately by the olecranon and distally by the line joining the radial and ulnar styloid processes; (8) the posterior hand area, comprising the dorsal part of the hand; (9) the anterior head and neck area, from the anterior craniofacial region, including the anterior part of the neck down, up to the level of C7; (10) the supraclavicular area overlying the area from the clavicle to C7; (11) the chest area, marked by the sternum medially, the clavicle above, a vertical line from the axilla laterally, and the inferior part of the pectoralis major muscle below; (12) the anterior shoulder area, corresponding to the anterior deltoid; (13) the anterior arm area, defined as the area between a horizontal line inferior to the anterior deltoid muscle and a line joining the lateral and the medial epicondyles at the cubital fossa; (14) the anterior forearm, limited proximally by the cubital fossa and distally by the line joining the radial and ulnar styloid processes; and (15) the anterior hand area, comprising the volar side of the hand. The frequency with which pain occurred in each region was used for data analyses.

Additionally, patients were asked to value the pain intensity using a 100-mm-long Visual Analog Scale (VAS) (0 = absence of pain, 100 = maximally imaginable pain).

Statistical Analyses

Normality of variables was assessed via the Shapiro–Wilk test. Parametric variables were expressed by their mean (standard deviation) and nonparametric variables by their median (interquartile range). A 2-way analysis of variance (ANOVA) test was employed to evaluate the extension of the referred pain area, in which the repeated measures were intensity (120%, 130%, 140%, and 150% PPT) and size of referred pain areas reported on back, front, and full body images,

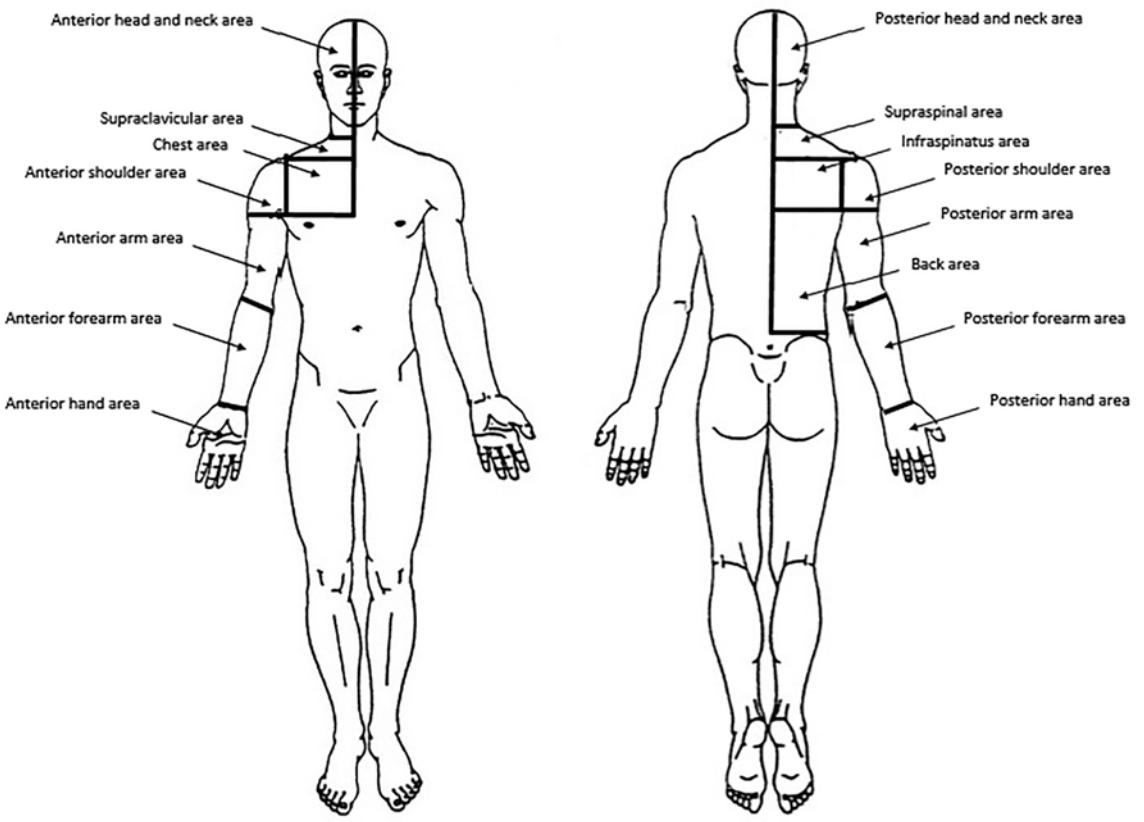

Fig. 1. *Sketch of the 15 predefined body regions to quantify the extension of referred pain following suprathreshold pressure stimulation on the infraspinatus muscle of the dominant side.*

whereas a 1-way, repeated measures analysis of variance (RM-ANOVA) was used to analyze pain intensity on a VAS. The effect of the sequence (ascending or descending order of stimulation) was tested prior to clustering the data via an unpaired-measures test (Mann-Whitney U test).

Variables measuring the referred pain areas and total number of body regions were converted into logarithms to obtain a normal distribution of the data. The total number of body regions was analyzed via a 1-way RM-ANOVA, whereas the frequency at which pain occurred in each body region was assessed via the Fisher exact test. Post hoc comparisons were conducted using the Wilcoxon signed-rank test with a Bonferroni correction.

An exploratory correlation analysis (Pearson correlation coefficient) was conducted to assess the relationship between the referred pain data (following their logarithmic transformation) and anthropometric, clinical, and psychological variables.

Statistical significance was set at $P < 0.05$. Considering a moderate effect size of 0.25, 2 groups, 4 repeated measures, a power of 90%, and a conservative estimated correlation of 0.33 between repeated measures, the sample size was estimated to be 52 patients. Estimating an effect size of 1.19 for the area of pain in patients with FM compared with controls, a post hoc power analysis determined that this sample size was enough for detecting potential intergroup differences. The software used for power calculations was G*Power version 3.1.9.4, (University of Düsseldorf, Düsseldorf, Germany) (41).

Results

Baseline characteristics of the patients are shown in Table 1. No withdrawal was recorded during the process.

An effect of sequence (ascending or descending order of stimulation) was observed on referred pain areas in the FM group at 150% PPT (Mann–Whitney U test: $P = 0.019$), but not in the control group.

Pain Sensitivity

Table 2 shows the recorded pain threshold values for both groups. The FM group registered lower PPTs than the control group (Student t-test, $P = 0.0001$).

Pressure-Induced Referred Pain

The referred pain areas were larger in the FM group compared with healthy patients: 120% PPT (Student t-test = 2.33, $P = 0.024$), 130% PPT (Student t-test = 4.34, $P = 0.001$), 140% PPT (Student t-test = 4.02, $P = 0.001$), and 150% PPT (Student t-test = 7.48, $P = 0.001$) (Table 3).

Within the FM group, no differences were found between the intensity of suprathreshold pressure stimulation and the size of referred pain areas (RM-ANOVA: F(3.63) = 5.5, $P = 0.135$) or pain intensity (RM-ANOVA: F(3.75) = 2.78, $P = 0.064$) (Table 3).

In the control group, differences were found in the total area of pain (front and rear view) when using different intensities to induce referred pain (RM-ANOVA: F(3.75) = 4.6, $P = 0.005$) (Table 3). The area of induced pain at 120% PPT was significantly lower than at 140% PPT (Bonferroni: $P = 0.023$). In terms of pain intensity as measured on the VAS, its value was significantly higher (RM-ANOVA: F(3.75) = 6.7; $P = 0.0001$) in the pressure ranges of 120% to 130% PPT (Bonferroni: $P = 0.024$) and 120% to 150% PPT (Bonferroni: $P = 0.004$) (Table 3).

In terms of the frequency at which pain occurred in each body area, the FM group showed a higher frequency in the following regions compared with the control group: anterior head/neck, supraclavicular, chest, anterior shoulder, anterior arm, anterior forearm, posterior head/neck, supraspinal, posterior shoulder, posterior arm, and back (Table 4). Additionally, only patients in the FM group reported referred pain in the following regions: anterior thigh (15.4%), posterior thigh (11.5%), anterior leg (15.4%), posterior leg (11.5%), foot dorsal (11.5%), and foot sole (3.9%), which were not reported as painful areas in the control group in any case.

Table 1. *Basal characteristics of the sample.*

	FM Group	Control Group
N (% women)	26 (84.6)	26 (84.6)
Age (years)	55.6 ± 8.8	55.7 ± 8.9
Height (cm)	162.5 ± 7.2	163.9 ± 5.1
Weight (kg)	69.4 ± 10.9	67.6 ± 9.9
Body mass index	26.4 ± 3.6	25.1 ± 3.3
Time since diagnosis (years)	11.9 ± 7.5	-
Catastrophizing	21.0 [13.0–29.0]	2.5 [0–7.0]
Quality of life	61.9 ± 16.0	-
Anxiety	33.6 ± 11.2	-
Depression	15.5 [11.0–21.3]	-

Data expressed by their mean ± standard deviation and median [interquartile range].

Table 2. *PPTs (mean ± standard deviation) bilaterally recorded for the 2 groups at the infraspinatus, supraspinatus, lower trapezius, and gastrocnemius muscles.*

Muscle		FM	Control	*P*
Supraspinatus	Dominant	1.54 ± 0.72	3.95 ± 1.21	0.0001
	Nondominant	1.44 ± 0.51	3.94 ± 1.59	0.0001
Infraspinatus	Dominant	1.50 ± 0.70	3.93 ± 1.43	0.0001
	Nondominant	1.52 ± 0.52	3.81 ± 1.67	0.0001
Lower trapezius	Dominant	1.60 ± 0.67	4.55 ± 1.95	0.0001
	Nondominant	1.55 ± 0.56	4.76 ± 2.18	0.0001
Gastrocnemius	Dominant	1.98 ± 0.84	3.95 ± 1.73	0.0001
	Nondominant	2.18 ± 1.01	4.35 ± 1.83	0.0001

The values of PPT are expressed in kg/cm^2.

The total number of body regions affected by pain was greater in the FM group compared with the control group during each of the suprathreshold pressure stimulations ($P = 0.0001$) (Table 5). In this regard, differences in the intensities to induce pain were observed both in the FM group (RM-ANOVA: F(3.60) = 3.7, $P = 0.016$) and the control (RM-ANOVA: F(3.75) = 3.9, $P = 0.011$), and significance was not reached in the post hoc comparisons using the Wilcoxon test with Bonferroni correction (Table 5).

Correlations

The potential association between the referred pain areas and anthropometric, clinical, and psychological variables was assessed, and a positive correlation was found between the body regions that experienced referred pain and pain catastrophizing in the FM group (Pearson r = 0.457, $P = 0.032$).

Table 3. *Median [interquartile range] area of pain after a 60-second pressure stimulation on the infraspinatus muscle of the dominant side.*

Pain Area												
	120% PPT	130% PPT	140% PPT	150% PPT	*P*	Pairwise comparisons*					
						1-2	1-3	1-4	2-3	2-4	3-4
FM	13,602 [5,669–23,869]	15,167 [5,603–23,645]	16,072 [6,581–28,396]	14,386 [7,306–33,892]	0.135	ns	ns	ns	ns	ns	ns
Control	1,356 [615–2,443]	1,835 [619–6,288]	2,520 [1,101–5,840]	1,845 [765–5,268]	0.005	ns	<	ns	ns	ns	ns
Pain Intensity											
	120% PPT	130% PPT	140% PPT	150% PPT	*P*	Pairwise comparisons*					
						1-2	1-3	1-4	2-3	2-4	3-4
FM	6.1 ± 1.7	6.3 ± 2.0	5.7 ± 1.9	6.8 ± 1.7	0.064	ns	ns	ns	ns	ns	ns
Control	3.7 ± 1.5	4.4 ± 1.9	4.3 ± 1.9	4.8 ± 2.0	0.000	<	ns	<	ns	ns	ns

The area is expressed by the number of pixels out of a total 602,931. Mean ± standard deviation pain intensity following a 60-second pressure stimulation on the infraspinatus muscle of the dominant side. *Bonferroni-adjusted pairwise comparisons: the symbol < indicates a significant difference ($P < 0.05$); ns, nonsignificant difference ($P > 0.05$).

Table 4. *Percentage of patients (n = 26 in each group) that reported pain in the different body regions when sustained pressure stimulation was applied on the infraspinatus muscle of the dominant side.*

	FM	Control
Anterior head/neck	30.8	3.9*
Supraclavicular	34.6	3.9*
Chest	42.3	3.9*
Anterior shoulder	53.9	19.2*
Anterior arm	46.1	15.4*
Anterior forearm	30.8	3.9*
Anterior hand	26.9	7.7
Posterior head/neck	61.5	7.7*
Supraspinal area	88.5	15.4*
Infraspinatus	100.0	84.6
Posterior shoulder	92.3	53.8*
Posterior arm	80.8	34.6*
Posterior forearm	50.0	26.9
Posterior hand	42.3	23.1
Back	84.6	3.9*

*indicates a significant difference ($P < 0.05$).

Table 5. *Median [interquartile range] body regions following a 60-second pressure stimulation on the infraspinatus muscle of the dominant side.*

Body Regions			
PPT	**FM**	**Control**	***P***
120%	4.0 [2.5–7.0]	1.0 [1.0–2.0]	< 0.001
130%	5.0 [2.5–8.0]	1.0 [1.0–3.0]	< 0.001
140%	5.0 [3.0–9.0]	2.0 [1.0–3.3]	< 0.001
150%	5.0 [4.0–8.0]	1.0 [1.0–3.0]	< 0.001

The final value expresses the number of regions out of a total of 15.

Discussion

This study is the first to explore the use of pressure-induced referred pain as a biomarker for sensitized pain mechanisms in patients suffering from FM syndrome. These patients reported referred pain body areas that were similar in size independently of the intensity of the applied suprathreshold pressure stimulation (120%, 130%, 140%, and 150% PPT). In contrast, the size of the referred pain areas increased in the control group only when the pressure was at 140% PPT, whereas pain intensity was not significantly greater. The potential contribution of these findings to the understanding of pain mechanisms in FM syndrome and their application to clinical practice are discussed hereafter. This study presents some limitations, among which is the variability found in the referred pain areas.

Pain Sensitivity

Patients suffering from FM presented a higher sensitivity to pain than those in the control group. These results are along the lines of findings from other studies that assessed the increase in pain sensitivity in musculoskeletal pain syndromes typically associated to CS, such as whiplash (16,17), tension-type headache (19,20), low back pain (21,22), osteoarthritis (23,24), carpal tunnel syndrome (25), or lateral epicondylalgia (26). Sensitized central pain mechanisms have been suggested to be common in both the increased pain sensitivity experienced by patients with FM and the earlier mentioned syndromes (9) in which different types of factors can play a role, such as altered descending modulation, psychological components, and changes in the presence of nociceptive neurotransmitters [increased levels of substance P (42,43), excitatory amino-acids (44), and

neurotrophins (45) in the cerebrospinal fluid of patients with FM].

However, peripheral mechanisms have also been suggested to account for high pain sensitivity, such as increased levels of substance P in muscle tissue (46). Moreover, spontaneously active C nociceptors (type IB) have been found in patients with FM in proportions similar to painful neuropathies and painful small-fiber neuropathies, which seems to be the only parameter that correlates with neuropathy painfulness (47). These similarities found between FM and peripheral neuropathies support the hypothesis that this spontaneous activity observed in the nociceptors C of peripheral nerves in patients with FM is enough to explain the pain sensations they experience (47). This outcome is in agreement with former studies that concluded that nociceptors C are directly involved in increased pain sensitivity (48-50), and hence their continuous stimulation contributes not only to its intensity but also to its development into chronic pain (51).

Pressure-Induced Referred Pain

Referred pain is likely driven by both peripheral and central mechanisms as it can be evoked in areas where the sensory input has ceased (52,53). Experimental pressure-induced referred pain has been suggested as a useful biomarker for assessing increased pain sensitivity of central pain mechanisms (31), and has been shown to be comparable to more traditional models, such as saline-induced pain, yet much less invasive, safer, and clinically transferable (31).

The aim of this study was to assess the distribution of referred pain areas evoked by different intensities of suprathreshold pressure stimulation in patients with FM. This method has been previously employed in trials (31,38) but never in patients suffering from FM syndrome.

Contrary to the outcome in the control group of this study, the referred pain areas described by patients in the FM group did not differ significantly at different pressure intensities. A series of neuroplastic changes are related to the sensitized pain mechanisms described for patients with FM syndrome, both at a peripheral [spontaneous activity of nociceptors C, such as type IB (47)] and at a central level [altered descending modulation, psychological factors, and changes in the concentration of nociceptive neurotransmitters (9,42-45)]. These changes produce an increase in pain sensitivity and can be involved in causing referred pain in multiple spinal segments (41,53). As a result, a slight pressure could result in areas of referred pain comparable to those produced by stronger pressures. This finding suggests that a mechanical stimulus slightly above the pain threshold can be a sufficient, simple, and safe method to assess the increased pain sensitivity that patients with FM experience.

Despite the known importance of sensitized pain mechanisms as a physiopathological basis for FM, the contribution of psychological factors cannot be obviated in these patients, which often experience depression, pain catastrophizing, or kinesiophobia (7,8). These cognitive and affective aspects are capable of influencing pain perception via the modulation of descending pathways (54) and are related to the amplification and extension of pain (55-58). The analysis conducted in this study on the correlation between the size of referred pain areas following suprathreshold pressure stimulation and psychological variables (depression, pain catastrophizing, and anxiety) showed a moderate direct association with pain catastrophizing. Thus it can be indirectly concluded that extensive areas of referred pain following suprathreshold pressure stimulation can indicate a greater level of catastrophizing and even become a predictive factor for it, revealing that these patients experience more grief and/or negative expectations in the face of a painful experience. Along these lines, former studies have found that high values of pain catastrophizing correlate negatively with the performance of descending modulatory systems (59), and that catastrophizing has a significant influence on the function of the prefrontal-dorsolateral cortex, which is related to pain modulation (60,61).

Clinical Implications and Future Research

The findings of this research show that referred pain induced by applying suprathreshold pressure stimulation can be a useful biomarker to assess the increase in pain sensitivity experienced by patients suffering from FM, with a 120% PPT being enough to assess pain mechanisms in FM. Future research could replicate this trial in other musculoskeletal pain syndromes typically associated with increased pain sensitivity and sensitized pain mechanisms, and also assess if the variability in the size of referred pain areas can provide a useful tool to assess the effectiveness of FM treatments.

Conclusions

The observed outcome suggests that a suprathreshold pressure stimulation of 120% PPT can be useful for evaluating sensitized pain mechanisms in patients with FM.

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